Patient specific factors predicting adherence and treatment effect of oral appliance therapy in obstructive sleep apnea

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Thesis for the degree of Philosophiae Doctor (PhD)
at the University of Bergen

Date of defense: 04.02.2022

Year: 2022

Title: Patient specific factors predicting adherence and treatment effect of oral appliance therapy in obstructive sleep apnea

Name: Kjersti Gjerde

Print: Skipnes Kommunikasjon / University of Bergen

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Scientific environment

The scientific work of my thesis was conducted as part of a PhD program at the Department of Clinical Dentistry, University of Bergen. The data collection and main scientific work was initiated and carried out at the Center for Sleep Medicine at Haukeland University Hospital. The work presented in this thesis was completed between January 2016 and July 2021.

In October 2017, I received a scholarship from the University of Bergen to conduct this PhD project. The principal Researcher, Anders Johansson (PhD), who is a Professor at the Department of Clinical Dentistry, University of Bergen, has been my main supervisor.

In addition, I had two co-supervisors:

Sverre Lehmann, MD, Associate Professor Haukeland University Hospital, Department of Thoracic Medicine, Center for Sleep Medicine, University of Bergen.

Bjørn Bjorvatn MD, Professor, Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital and Department of Global Public Health and Primary Care, University of Bergen.

The supervisors have been inspiring cornerstones in the scientific environment. I found knowledgeable and supportive colleagues who stimulated my curiosity, and showed the way with high quality research and international networking.

Acknowledgements

First, I would like to thank all the participants in the studies comprising this thesis. Without your cooperation and willingness to contribute, this work could not have been performed. I am grateful to the Department of Clinical Dentistry, Faculty of Medicine, which gave me the opportunity to conduct this thesis through the PhD program at the University of Bergen.

During my PhD-period I have been lucky to receive guidance and support from many people. I want to thank:

My main supervisor, Anders Johansson, for his patience and support during these years of exciting work. Thank you for always being positive and encouraging and also very enthusiastic about sharing your knowledge with me.

My two co-supervisors Sverre Lehmann and Bjørn Bjorvatn for always giving me constructive and helpful feedback when I needed it.

Thank you to my colleagues at the Center for Sleep Medicine, Morten Eirik Berge, Inga Zilinskaite, Thomas Berge, Ingvild Saxvig, Tom Aasnes, Siri Waage, Mona Grundeland and Hilde Kristin Tveit for good discussions and practical help and always being positive and supportive.

Thank you to all my friends for your support and encouragement in these years. I am really looking forward to spend more time with you in the time to come.

Thank you to my large and amazing family for your support and care.

Last, but not least thank you to my precious children Jenny, Johanne, Kyrre, Sondre and Mads for believing in me and always being proud of me.

Jan, my dear husband, soulmate and shotgun I would not have managed this without your support. Thank you.

Abbreviations

AASM	American Academy of Sleep Medicine
AHI	Apnea-hypopnea index
BMI	Body mass index
BQ	Berlin Questionnaire
CI	Confidence interval
CPAP	Continuous Positive Airway Pressure
CVD	Cardiovascular Disease
ESS	Epworth Sleepiness Scale
ICC	Intraclass correlation coefficient
MAD	Mandibular advancement device
OA	Oral appliance
ODI	Oxygen desaturation index
OR	Odds ratio
OSA	Obstructive sleep apnea
OSAS	Obstructive sleep apnea syndrome
PG	Polygraphy
PSG	Polysomnography
RDI	Respiratory disturbance index
REM	Rapid eye movement
RLS	Restless legs syndrome
SD	Standard deviation
SRBD	Sleep-related breathing disorder
TRD	Tongue-retainer device

Abstract

The overall objective of this thesis was to generate new knowledge about treatment with mandibular advancement devices (MAD). MAD. Adherence and MAD treatment effects were measured in patients suffering from obstructive sleep apnea (OSA). Continuous positive airway pressure (CPAP) is the first-line treatment for OSA, and only patients who were non-adherent to CPAP were included in this project.

The first study assessed the effect of MAD on the apnea/hypopnea index (AHI) of an individually adjusted MAD in patients with moderate(n=82) and severe (n=34) OSA.. Nocturnal respiratory polygraphic recordings (PG) were performed at baseline and 12-month follow-up, and reduction in AHI was the primary outcome for success. The overall treatment success rate was 75%, and there was no significant difference in success rates between the moderate and severe categories. Low pre-treatment oxygen saturation (SpO2 nadir) predicted MAD failure in the multiple regression analysis.

The aim of the second study was to test whether a built-in MAD sensor was reliable compared to self-reported MAD use for one month. Patients (n=80) with all grades of OSA were included. The relative reliability was high with an intraclass coefficient (ICC) at r= 0.847.

The aim of the third study was to measure AHI change, MAD adherence in patients with all grades of OSA, and to identify partner-specific factors related to adherence. The mean AHI was reduced to half at 8 month follow-up, and sensor-measured adherence rate at follow-up was 60.1%. Mean reduction in AHI was significantly greater in the "good" than in the "poor" adherence group. From the partner perspective, good adherence to MAD was associated with signifigreater positive effects on their relationship and being able to share bedroom again.

We conclude that MAD seems to be an effective treatment alternative for all grades of OSA. Low SpO_{2nadir} predicted a poor effect from MAD. Adherence to MAD could be reliably measured with a built-in sensor. MAD adherence is related both to the treatment effect and bedpartners' motivational influence. Their attitude and support may be a hidden resource for improving adherence to MAD in the treatment of OSA.

List of Publications

Paper 1

Gjerde, K., Lehmann, S., Berge, M. E., Johansson, A. K., & Johansson, A. (2016). Oral appliance treatment in moderate and severe obstructive sleep apnoea patients non-adherent to CPAP. *J Oral Rehabil*, 43(4), 249–258.
doi:10.1111/joor.12376

Paper 2

Gjerde, K., Lehmann, S., Naterstad, I. F., Berge, M. E., & Johansson, A. (2018). Reliability of an adherence monitoring sensor embedded in an oral appliance used for treatment of obstructive sleep apnoea. *J Oral Rehabil*, 45(2), 110–115.
doi:10.1111/joor.12584

Paper 3

Gjerde, K., Lehmann, S., Bjorvatn, B., Berge, M., Thuen, F., Berge, T., & Johansson, A. (2021). Partner perceptions are associated with objective sensor-measured adherence to oral appliance therapy in obstructive sleep apnea. *J Sleep Res*, e13462.
doi:10.1111/jsr.13462

1. Introduction

1.1 General considerations about sleep

Of all living species on the Earth who have been studied, sleep occurs in either larger or smaller parts of the day and the night. This may indicate that sleep actually has been present at the same time as life itself first occurred. The fact that sleep has been, and still is, an interesting condition which has followed us from genesis through the evolution, may further indicate that the benefits of sleep probably outweigh any disadvantages of sleeping. Recent scientific findings in sleep research have enhanced our understanding of sleep. It has turned out that sleep is much more complex and important than previously believed (Ochab et al., 2021) (Sweetman et al., 2021). It has until today been found that sleep has a number of benefits for vital functions, such as improving brain functions, rebuilding the body's tissues and immune system and getting rid of biological waste products during sleep. The importance of sleep for people's general well-being and health status has been under-communicated until recently. Nowadays, sleep-related problems have become a major health challenge for many people and as well for society. These include increased sick leave, reduced work capacity and an increased risk of becoming involved in traffic accidents. There are many people of all ages, who suffer from sleep problems during different stages in their lives, and we consider as many as 10%–15% of these have serious and long-term sleep problems that need to be treated (Sweetman et al., 2021). In connection with the Covid-19 pandemic, the prevalence of undiagnosed sleep breathing disorders was as high as 79% in patients with acute respiratory stress disorder (Labarca et al., 2021). But unfortunately, many people who have sleep problems do not seek medical help, and therefore remain undiagnosed and untreated. As much as 80% of the general population might be undiagnosed (Sweetman et al., 2021). However, it is important to remember that sleep problems often are associated with a number of other co-morbidities.

The high prevalence of co-morbidity in obstructive sleep apnea (OSA) patients was also mirrored in a recent literature study from Canada. They found that patients hospitalized with heart disease exhibited a prevalence of OSA at 48% (Suen et al.,

2020). Looking at this from the other angle as primarily an OSA diagnosis, 94% of OSA patients had one or more co-morbidities (Testelmans et al., 2021). Hypertension was one of these conditions. This study indicates that there may be a knowledge gap about the consequences of OSA between different medical specialities, and that effective OSA treatment may influence OSA co-morbidities positively.

"International Classification of Sleep Disorders" second edition ICD-2; is one of the most widely used classification systems for sleep disorders. Based on epidemiological studies, the most common sleep disorders are: (1) Insomnia, (2) Sleep-related breathing disorder (SRBD) and (3) Restless legs syndrome (RLS). With regard to these three most common sleep disorders, a study from 1993 is one of the frequently cited references in relation to SRBD (Young, 1993). In this study with 602 people, 24% men and 9% women were in the risk group for SRBD, and in the same group, 4% men and 2% women were diagnosed with SRBD, and these patients also had extreme daytime fatigue. Sleep-related respiratory disorders are characterized by an unusual breathing pattern during sleep and consist of three subgroups: (1) central sleep apnea syndrome (CSA), (2) obstructive sleep apnea syndrome, and (3) sleep-related hypoventilation / hypoxia syndrome. The characteristic of CSA is the absence of breathing movements and ventilation efforts during sleep (Westchester, 2005). The etiology is unclear, but still some researchers suggest that this disorder is due to cardiac problems or central nervous system dysfunction associated with a ventilatory controller mechanism (Arzt & Bradley, 2006).

A polysomnography (PSG) registration has been seen as necessary to verify this diagnosis (Kimoff, 2015). There are four types of CSA syndromes, which all exhibit an abnormal breathing pattern. Primary central sleep apnea is characterized by varying and recurrent cessation of respiration, but no ventilation efforts (Guilleminault et al., 1996); Cheyne-Stokes sleep apnea has a breathing pattern of recurrent apneas, hypopneas or even both episodes, and then a prolonged episode of hyperpnea which is deep and rapid respiratory efforts, the characteristic crescendo-decrescendo pattern; also called the Cheyne-Stoke breathing pattern (Hall et al., 1996) (Naughton, Benard, Tam, Rutherford, & Bradley, 1993).

The third type of CSA is high-altitude periodic breathing which is a sleep disorder that is caused by acute mountain sickness (Weil, 2004)

The fourth type is called sleep-related hypoxia-disease and may occur during sleep when the patient experiences respiration problems. This disease is normally associated with obesity and patients often have BMI> 35. Clinically this is known as hypoventilation syndrome (OHS), and results in too much carbon dioxide and too little oxygen in the blood (Laub & Midgren, 2007).

Since obstructive sleep apnea is the sleep-related breathing disorder in which dentists may play a role in treatment and diagnosis, I will concentrate on OSA in my thesis.

1.2 Etiology and diagnosis of OSA

Obstructive sleep apnea (OSA) involves cessation of airflow during ongoing inspiratory activity, caused by complete or partial collapse of the upper respiratory tract (Fig.1). This will cause reduced ventilation during sleep, even if there is normal breathing effort. The severity of OSA is indicated by the number of breathing cessations per hour, expressed as the apnea-hypopnea index (AHI), which indicates the number of apneas and hypopneas during sleep.
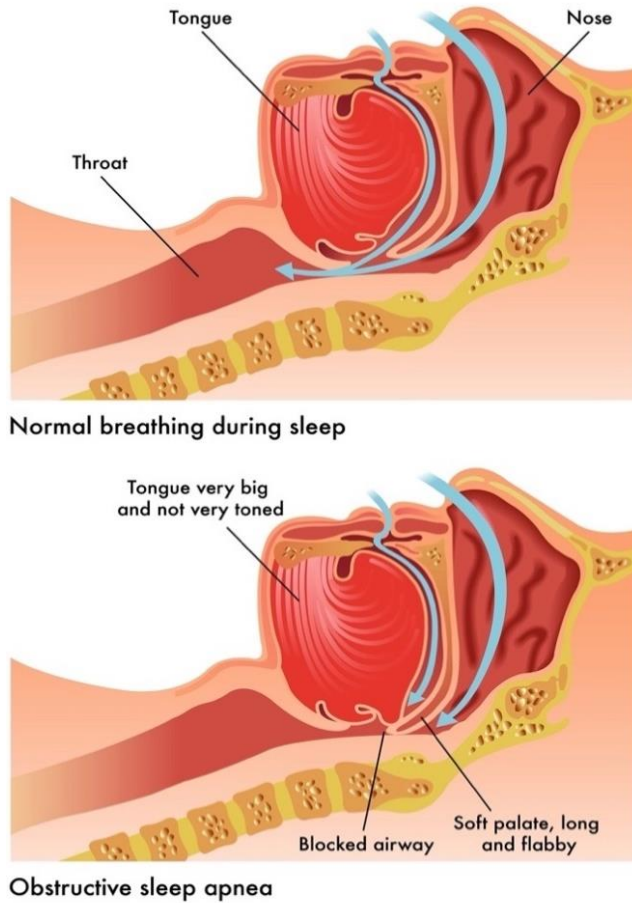
Fig. 1. *Illustration of normal breathing and obstructive sleep apnea*

(By permission from SomnoMed)

We define an apnea as a breathing obstruction with at least 90% reduction in airflow, lasting more than 10 seconds, and a hypopnea as a partial breathing obstruction with at least 30% reduction in airflow, lasting for at least 10 seconds and a decrease in oxygen saturation of at least 3% (Berry et al., 2012). Both apneas and hypopneas cause a decrease in oxygen saturation in the blood. It is common to use a pulse oximeter attached to the patient's finger to measure oxygen saturation. This measurement forms the basis for an index that expresses the oxygen desaturation index (ODI), which

corresponds highly with the AHI. The severity of sleep apnea is commonly divided by the number of apnea and hypopnea per hour; normal respiration is AHI <5 healthy, AHI = 5–14.9 mild grade of OSA, AHI = 15–29.9 moderate grade of OSA, AHI> 30 severe grade of OSA (Berry et al., 2012).

When establishing the diagnosis of obstructive sleep apnea, several examination methods and outcome measures are used. Mainly three groups of technical investigations are used for diagnosis of obstructive sleep apnea during sleep (Bjorvatn, 2012)

(1) Examination of one parameter, i.e., pulse oximetry. This is the simplest and easiest way to investigate respiratory disorders. This method alone is not recommended, because apneas and hypopneas will not be registered, resulting in a low sensitivity for diagnosing mild to moderate OSA. But pulse-oximetry can be useful in a follow-up period of sleep apnea patients.

(2) Examination of several parameters during sleep; i.e., respiratory polygraphy (Fig.3) which measures airflow, breathing movements, sleeping position and breathing pressure. This can be done by using a type 3 portable monitor for example NOX-T3 ™, which can differentiate between apneas and hypopneas as well as obstructive and central apneas. The type 3 monitor is an important instrument to use, because of its ability to determine both AHI and oxygen desaturation (ODI) during sleep. PG is currently the most commonly used method for diagnosing obstructive sleep apnea in Norway.

Normal sleep is characterized by even breathing waves which are moving in the same pattern through the nose, thorax and abdomen (Fig.2). An obstructive breathing is characterized by reduced airflow and an uneven breathing pattern with an upper respiratory blockage in a paradoxing breathing pattern. In addition, there is a reduction in oxygen saturation in the blood. In a central apnea there is no inspiratory work throughout the event (Fig.3).
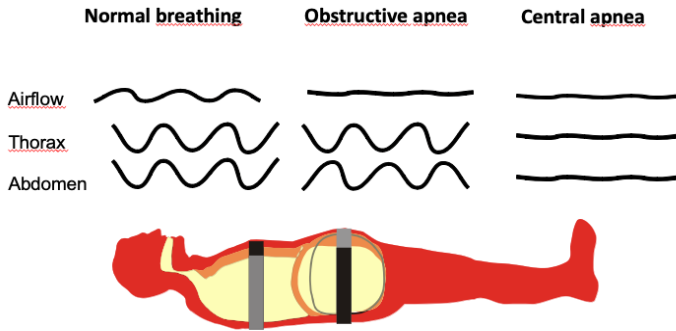
Fig. 2. *Normal sleep, obstructive apnea and central apnea.*
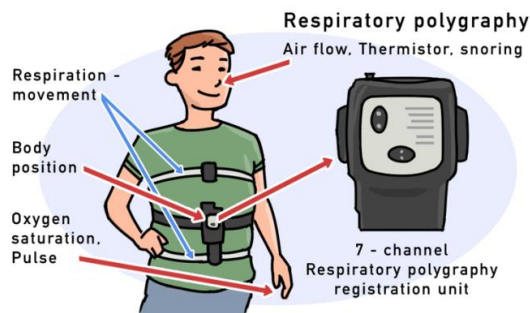
Fig. 3. *Respiratory polygraphy (PG)*

(By permission and illustrated by Thomas Madsen)

(3) Polysomnography (PSG) is an advanced multi-channel test, adding several channels to a common respiratory PG, including examination of the electroencephalogram to define the various sleep stages during sleep. PSG can be used to diagnose, or to rule out, other types of sleep disorders like periodic limb movement disorder. A lot of information about sleep can be retrieved from a PSG examination compared to a PG, such as sleep onset latency (SOL), the REM-sleep onset latency, number of awakenings

during sleep-period, the total sleep duration, duration and percentage of sleep stage and number of arousals. (Berry et al., 2012).

According to the guidelines from the American Academy of Sleep Medicine (AASM), only PSG or PG are recommended to validate a diagnosis of OSA. Clinical tools, questionnaires and prediction algorithms are not recommended to be used alone to establish the OSA diagnosis.

The table below shows the recommended AASM diagnostic criteria for obstructive sleep apnea for adults. The criteria are based on the International Classification of Sleep Disorders, 3rd edition, (Ito & Inoue) 2015,.

Table 1. *The table below summarizes the AASM algorithms of the two pathways to an OSA diagnosis.*

EITHER	
	Presence of at least one typical symptom: • Daytime sleepiness (ESS > 10), unfreshing sleep, fatigue or insomnia • The patient wakes up holding his breath, gasping or choking • The bedpartner reports loud snoring, breathing interruption or both during sleep.
AND	
AHI > 5	Polysomnographic recording show more than 5 obstructive scoreable respiratory events per hour.
OR	
AHI > 15	Polysomnographic recording shows 15 or more scoreable respiratory events (apnea or hypopnea) per hour of sleep.

In addition to the technical measurement methods mentioned, various questionnaires can be used as supplementary tools when we are suspecting OSA and do not have a PG or PSG available to detect those who are at risk of developing OSA, who subsequently may be referred to undergo sleep studies. There are many different screening tools like Epworth Sleepiness Scale (ESS), Berlin Questionnaire (BQ), STOP-Bang

questionnaire, Pittsburg Sleep Quality Index and NoSaS Score, which can be utilized until the final diagnosis is determined by the recommended measurements methods (PG or PSG) (Marti-Soler et al., 2016) (Verse, Baisch, Maurer, Stuck, & Hörmann, 2006); (Carvalho et al., 2020) (Liamsombut et al., 2021).

It is important, upon suspicion of OSA to follow up with further sleep examination. This because OSA is associated both with increased risk of sudden death for all causes, and as well for cardiovascular adverse events (Heilbrunn, Ssentongo, Chinchilli, Oh, & Ssentongo, 2021). It seems that there is an OSA severity-dependent pattern, with doubled risk for sudden death in persons in the severe OSA category.

Excessive daytime sleepiness (EDS) is regarded as a prevalent symptom that affects activities and quality of life during the day. It is typical that the person is unable to remain alert and awake during the hours that one normally is awake. Therefore, EDS may be an indicator that the person is suffering from an inadequate amount of sleep, or a fragmented or disrupted sleep or another sleep disorder. Epworth Sleepiness Scale (ESS) is one of several screening tools used to map excessive daytime sleepiness, even if this tool has variable diagnostic performance (Basille, Baud, Andrejak, Basille-Fantinato, & Jounieaux, 2020). A thorough clinical history is very important, and in addition, any loud snoring and /or extreme daytime fatigue should be registered. This can be done in conversation with the patient and /or partner, and also by using suitable questionnaires such as ESS, BQ, GOAL, Stop-Bang and NoSaS Score as supplementary tools (Duarte, Magalhães-da-Silveira, & Gozal, 2020). After this, a clinical examination of the patient is performed, including blood pressure and weight measurement, nose and throat inspection and relevant blood sample test as well as allergy tests if indicated.

1.3 Incidence and prevalence of OSA

OSA is a widespread and prevalent disorder in the general population, but also highly prevalent in some specific disease-related and population-based subgroups (Heinzer et al., 2015) (Tufik, Santos-Silva, Taddei, & Bittencourt, 2010). It is estimated that more

than 1 billion people are suffering from the global burden of OSA (Benjafield et al., 2019).

The incidence of OSA has been increasing in recent years, and in a large survey of US military service personnel from 2005 to 2019, the annual incidence-rate increased significantly from 11.8 in 2005 to 333.8 per 10.000 persons in 2019. Most of the rise in incidence has particularly taken place during the last decade (Moore, Tison, Palacios, Peterson, & Mysliwiec, 2021).

The prevalence of OSA varies with different factors, and the increasing prevalence of OSA seem to be a global problem (Twells, Gregory, Reddigan, & Midodzi, 2014) (Zaninotto, Head, Stamatakis, Wardle, & Mindell, 2009) (Cámara & Spijker, 2010; Young & Peppard, 2005).

This phenomenon could partly be explained by the increasing rates of obesity and old age in the population, which are considered as major risk factors for developing OSA (Young, Peppard, & Taheri, 2005). It could also be due to improved measurement methods and changes in definitions for the classification of respiratory events, which have undergone a change in diagnostic thresholds during the last decade (Berry et al., 2012) (Ruehland et al., 2009). The study named: "The New AASM Criteria for Scoring Hypopneas: Impact on the Apnea Hypopnea index", shows that using different definitions when scoring a hypopnea entails differences in AHI, and consequently affects the process of establishing diagnosis of the patients (Ruehland et al., 2009). If the health personnel (doctors/nurses) use 3% as cutoff value while scoring a hypopnea/apnea, more cases of obstructive sleep apnea will be diagnosed compared to if a cutoff of 4% is used. This is why determining the exact prevalence of OSA in the general population is difficult, but still very important.

In a systematic review from 2017 (Senaratna et al., 2017), the authors aimed to determine the prevalence of OSA in adults in the general population and assess how the prevalence varied between different population sub-groups. This review consisted of 24 studies: 14 from Europe, 5 from North America, 2 from New Zealand and Australia, 1 each from Latin America, East Asia and South Asia. They exhibited great methodological heterogeneity. When prevalence was calculated with an AHI ≥ 5

events/hour, the overall population prevalence ranged from 9% to 38%. Prevalence increased with increasing age, and in some elderly groups (60–85 years), it was as high as 90% in men and 78% in women (Senaratna et al., 2017).When studies were limited to moderate OSA with an AHI ≥ 15 events/hour, the prevalence in the general adult population (30–65 years) ranged from 9% to 17%, and was as high as 49% in the older ages. Briefly summarized; advanced age, male sex and high body mass index were all significantly associated with a high OSA prevalence. In addition, the authors of the latter study call for generating consensus on methodology and diagnostic thresholds to define and diagnose OSA in epidemiological studies across all regions and countries.

In Norway, a survey with the Berlin Questionnaire in the age group 30–65 years, 24.3% were estimated to have a high risk of suffering from OSA (Hrubos-Strom et al., 2011). And in the same study, the estimated prevalence of OSA in the clinical sample group which underwent PSG, were 16% for AHI ≥ 5 and 8% for AHI ≥15. In a study from Chile using PG at home OSA (AHI ≥5) occurs twice as often in men as in women (62% versus 31%) and for OSA (AHI ≥15) the prevalence was 21% for men and 13% for women (Saldías Peñafiel et al., 2020), and 34% vs 17% (Peppard et al., 2013). In another review from 2015 of eleven prevalence studies, the average prevalence of OSA defined as AHI ≥5 and confirmed by PSG or PG, was a mean of 22% (range, 9–37%) in men and 17% (range, 4–50%) in women.

Excessive daytime sleepiness, which is commonly considered as a risk factor and also a symptom of OSA, occurred surprisingly in only 6% (range, 3–18%) of men and in 4% (range, 1–17%) of women (Franklin & Lindberg, 2015).

A supine sleeping position seems to increase sleep apnea episodes (Chung, Enciso, Levendowski, Westbrook, & Clark, 2010). And a logical explanation may be that the soft tissues at the anterior of the neck and the gravity compress the upper airways, and particularly in obese persons. Interestingly, this only seem to occur in adults, but not in children (Verhelst et al., 2019).

During REM sleep OSA typically worsens in adults, except in patients with positional obstructive sleep apnea (POSA) (Young & Collop, 2014). Episodes of apnea or hypopnea typically occur during REM sleep, and these episodes seem to be longer and

associated with a more profound drop in oxygen saturation than in non-REM sleep (Rishi & Rishi, 2021).

1.4 Risk factors and co-morbidities of OSA

Risk factors for the development of OSA are many and complex. The dramatic increase in OSA prevalence is larger than what can be explained by a single factor, either the obesity epidemic, older age or lifestyle alone.

1.4.1 The obesity pandemic

Obesity is probably the most common modifiable risk factor for developing of OSA. The proportion of overweight persons in the Norwegian population has increased by approximately 10–15% during the period from 1984 until 2008, especially among men (Midthjell et al., 2013).

Figure 4 shows how the incidence of obesity has increased steadily in men and women (40–69 years) in Tromsø over the past 20 years until 2016.
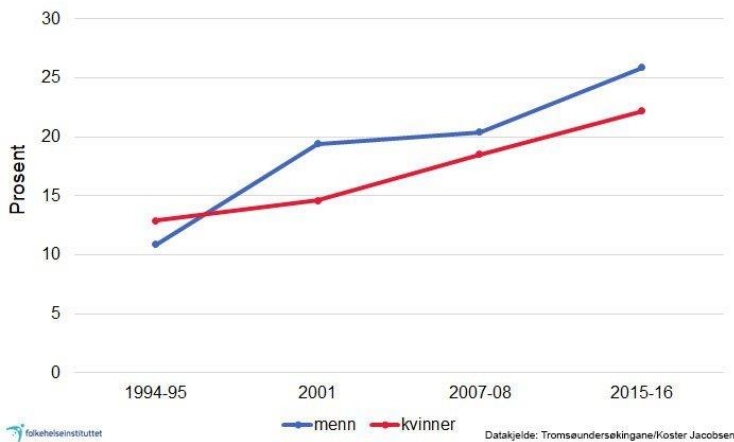
Fig. 4 *Percentage of obesity (BMI ≥ 30kg/m^2) from Tromsø Survey.*

(By permission from FHI- Folkehelseinstituttet)

Most likely, several factors such as increased awareness of the diagnosis, improved diagnostic tools, an aging population, physical inactivity, lifestyle and diet contribute to the increasing OSA prevalence rates globally (Fig.5).
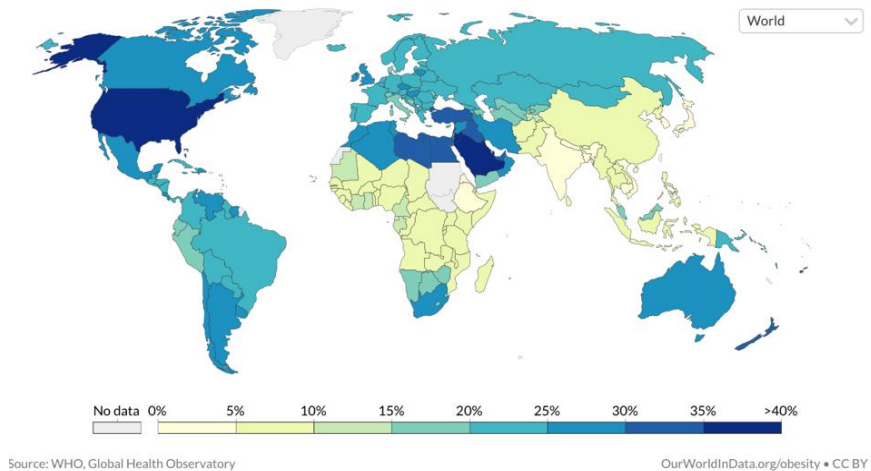
Fig. 5 *The share (%) of obesity in the global adult population in 2016*

(By permission from FHI (Folkehelseinstituttet).

Patients may have OSA with no subjectively reported symptoms and may sometimes be discovered when screening for other diagnoses (Ooi et al., 2021). Patients with severe obesity are at a very high risk of having moderate or severe OSA. In particular if they are men, older, obese, and/or with type 2 diabetes, then an underlying diagnosis of OSA should be suspected (Ahlin et al., 2019; Kimoff, 2015). In addition, OSA patients have increased risks of metabolic syndrome, and gastroesophageal reflux (Tawk, Goodrich, Kinasewitz, & Orr, 2006) (Okobi et al., 2021) (Ooi et al., 2021).

A recent cohort study of obese patients (mean BMI = 47.1, ±8.2) (Ahlin et al., 2019) found the prevalence of moderate or severe OSA to be as high as 96.3%. Sleep apnea is almost twice as common in men as in women (Testelmans et al., 2021). However, this gender difference is reduced after the menopause (Tufik et al., 2010).

1.4.2 Cardiovascular risks and co-morbidities

Cardiovascular disorders (CVD) such as high blood pressure, stroke and heart attack are linked to OSA, and this can cause major health consequences and sudden death for the person concerned (Tveit et al. 2018). However, it is often difficult to define whether OSA is causing co-morbidities or is only associated with them. In a large retrospective study, it was found that patients first developed hypertension and then developed OSA later in the course of the disease (An et al., 2021). Strong correlations have also been found between OSA and hypertension (Testelmans et al., 2021), and in a case-series study, the authors found significant reductions in both systolic and diastolic blood pressure with MAD use for 3 months and 3 years, respectively (Andrén, Sjöquist, & Tegelberg, 2009)

The cardiovascular consequences of OSA may be lethal, and with significantly higher risk for cardiovascular mortality in OSA patients, were reported (Heilbrunn et al., 2021).

1.4.3 Other risk factors

Alcohol and smoking appear to increase the risk of sleep apnea as well as various metabolic diseases and Downs Syndrome (Saldías Peñafiel et al., 2020). In addition to obesity, gender and age, intrinsic factors like anatomical differences in the upper airway volume such as narrow airways and underdeveloped lower jaw ("Birdface") (Fig.6) turned out to be an important risk factors for developing obstructive sleep apnea. (Marcussen et al., 2015)
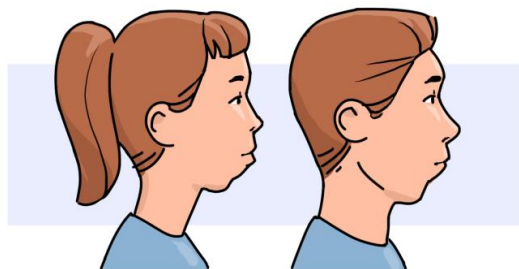
Fig. 6 *Underdeveloped underjaw, "birdface"*

(By permission and illustrated by Thomas Madsen)

In a pilot study from 2017 with 30 randomly selected patients, the authors' intention was to measure changes in the upper airways volume after orthognathic surgery. The reason for this was because a reduced volume of the internal skeletal dimensions of the face can be an important cause of sleep apnea. The result of this study suggested that bi-maxillary orthognathic surgery increased the upper airways volume parameters from 83 mm^3 to 102 mm^3 in some patients, but some patients still have impairment of the airways after surgery. However, more studies are needed to shed light on this issue (Marcussen, Stokbro, Aagaard, Torkov, & Thygesen, 2017).

1.5 Symptoms and consequences of OSA

Health problems affect mainly ourselves, but conditions like OSA may affect our interaction with other people too. Symptoms of sleep apnea appear both during the night and during the day (Tegelberg, Nohlert, Bergman, & Andrén, 2012). At night, patients may experience poor sleep quality, loud snoring, sweating, reflux, sudden awakenings and feelings of suffocation. In addition, they may have a tired and irritable partner who has been kept awake by their respiration problems during the night (Fig.7). Consequently, symptoms of sleep apnea may also indirectly affect both the bedpartner's and patients' working ability during the day. Extreme daytime fatigue, concentration problems, headaches, dry mouth, irritation, depression, and decreased libido are all symptoms that affect the psychosocial interaction.
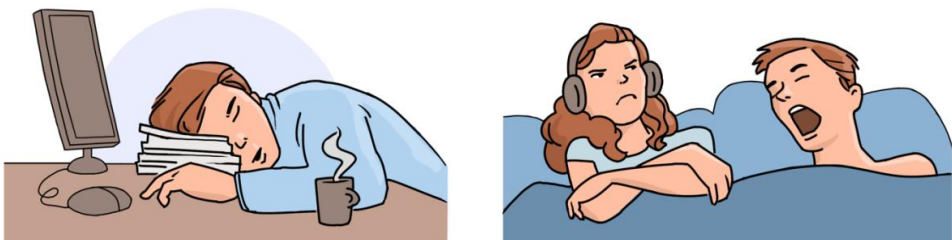
Fig. 7 Extreme daytime sleepiness and disturbing of bedpartner during night.

(By permission and illustrated by Thomas Madsen)

OSA is associated with driving performance-related traffic accidents. Several studies have found that OSA affects the driver's ability in a negative way, and that OSA represents an important risk factor for traffic accidents, especially with moderate and severe OSA, and a high degree of sleepiness, driving capacity could be negatively affected (Bîrleanu, Rusu, & Mihaescu, 2010). Sleepiness may account for up to 20% of traffic crashes on monotonous roads, and increases the risk of falling asleep behind the wheel while driving (Strohl et al., 2013) (Fig.8).

As a consequence of the fact that OSA represents an important risk of motor accidents, the European Union (EU) has prepared new rules to contribute to reduce the risk of such accidents. The rules developed standards of management for doctors authorized to perform medical examinations of drivers regarding their driving license, in case of OSA. The new directive on driving licenses, which was in force from December 31, 2015, was mandatory for all member states in the EU (Bonsignore et al., 2016). Even though OSA increases the risk of accidents, the disease is only associated with EDS in approximately 50% of the OSA patients (Strohl et al., 2013). Reports vary somewhat in their interpretation of the available scientific evidence. But greater OSA severity seem to be associated with increased daytime sleepiness (Bjorvatn et al. 2015) and driving risk (McNicholas & Rodenstein, 2015). But many other factors like shift work, medication, alcohol, sleep duration and poor sleep quality can cause sleepiness, and this is important to be aware of, especially for professional drivers (Di Milia et al., 2011). Subjective excessive daytime sleepiness in OSA patients is usually assessed with questionnaires. But this relies on subjective data, and objective evaluation is expensive and not easy to organize on a large scale (Bonsignore et al., 2016).

Fig. 8*. A tired driver who risks an accident.*

(By permission and illustrated by Thomas Madsen)

The American Thoracic Society officially convened a multidisciplinary team to update and grade the recommendations in the guidelines from 1994 about the relation between sleepiness, sleep apnea and driving risk. A strong recommendation was made for treatment of confirmed OSA with CPAP, rather than no treatment. Additional suggestions included routinely determining the driving risk by monitoring sleepiness, educating patients about the risk of excessive sleepiness and encouraging clinicians to become familiar with relevant laws (Strohl et al., 2013).

Thus, the burden of OSA(Fig.9) has in addition economic consequences in terms of production losses, increased risk of being involved in traffic accidents and reduced quality of life (Siedlecka et al., 2020; Tarasiuk & Reuveni, 2013).
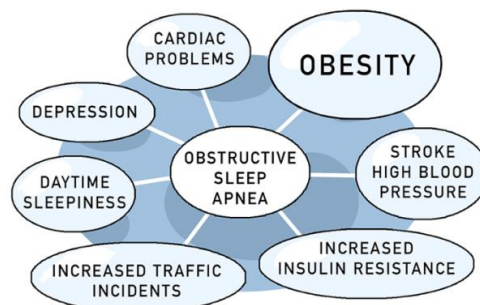
Fig. 9*. Comorbidities and consequences of obstructive sleep apnea.*

(By permission and illustrated by Thomas Madsen)

1.6 Treatment

The most common treatment options for obstructive sleep apnea can be divided into three main groups:

1) Continuous positive airway pressure

2) Mandibular advancement device

3) Conservative treatment/ lifestyle interventions

1.6.1 CPAP history / evolution and treatment

The history of CPAP therapy dates back to the early 20th century when researchers first began studying different sleep patterns. In the 1920s, researchers of that time agreed upon the fact that brain waves vary in humans, both when they are awake and when they are asleep. REM sleep was discovered and first described in 1953 by Professor Nathaniel Kleitman and his student Eugene Aserinsky (Kleitman & Aserinsky 2003). They defined rapid eye movement and linked it to dreams. REM sleep was further described by researchers including William Dement and Michel Jouvet. (Dement & Pelayo, 2018). Sleep analyses became more common, and researchers began to look closer at sleep disorders.

The first description of sleep apnea syndrome was done by the American doctor Christian Guilleminault and colleagues in 1973, when they described disrupted sleep breathing in non-obese patients. Some years later in 1978, Guilleminault observed obstructions in the airways during sleep, and how these obstructions had a negative effect on sleep. The result was published in the journal *Chest* (Remmers, Younes, & Baker, 1978). After testing positive airway pressure on dogs with promising results, Dr. Collin Sullivan began testing this treatment on humans. When Colin Sullivan et al., published an article (Sullivan, Issa, Berthon-Jones, & Eves, 1981) in The Lancet showing that a CPAP could reverse OSA, this led to great interest in the sleep research community. The first commercial breathing machine, continuous positive airway pressure (CPAP), became available in the United States in 1980. However, Dr. Colin Sullivan has been credited by others for inventing the CPAP machine in 1990. A

machine with a specially designed mask covering the nose and mouth was introduced. This resulted in better comfort for the patient and improved treatment results.

The CPAP is a breathing machine that provides a continuous positive airway pressure in the airways, and it has the ability to keep the airways open during sleep. A mask covering the nose or sometimes both the nose and mouth, and is connected by hoses to the CPAP, and the air pressure is brought down through the upper part of the pharynx passing the soft palate and tongue, and further down to the upper respiratory tract and into the lungs (Fig.10). Compared to the atmospheric pressure, the intraluminal positive pressure from CPAP dilates the upper airways. At the same time as the upper airways open, sometimes often called a "pneumatic splint", a reduction in the activity of the smooth muscles of trachea is caused and the air can pass freely to the lungs (Zhao & Redline, 2015).
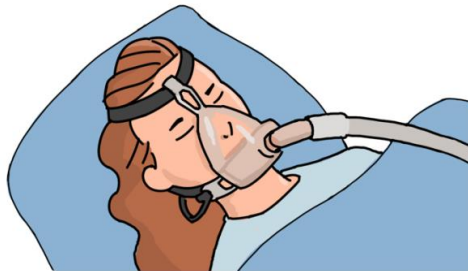
Fig. 10. *Woman sleeping with her CPAP*.

(By permission and illustrated by Thomas Madsen)

At the end of 2014, more than 1 million people in the world used a CPAP machine at home (Demko, 2018). CPAP therapy actually began as a short-term alternative to surgery, but today the CPAP machine has become an evidence-based, and non-invasive treatment method for OSA worldwide (Varga et al., 2020). Surgery was commonly used until 2008, but the lack of positive long-term results has led to a decline in the use of surgery in OSA patients (Sutherland & Cistulli, 2019).

Continuous positive airway therapy is often prescribed to treat OSA, and there is no doubt that successful CPAP treatment of obstructive sleep apnea can result in positive treatment outcomes for the patient. It has been shown that CPAP therapy improves extreme daytime fatigue, the number of respiratory cessations, sleep quality, cognitive function, and the patient's quality of life (Wang et al., 2013).

Although the CPAP has been proven to be effective, some patients are unable to use CPAP due to discomfort and side-effects. The most common side-effects are dry nose, leakage from the mask, pressure ulcers, eye irritation and claustrophobia (Weaver & Sawyer, 2010). And in some patients the CPAP may be less effective in preventing the breathing cessations during REM sleep (Rishi & Rishi, 2021).

1.6.2 Mandibular advancement device (MAD)
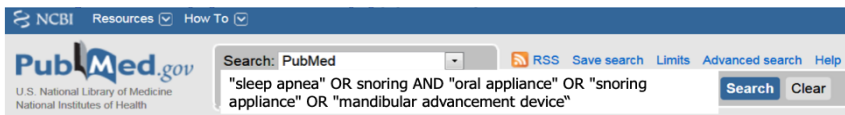
Different OA have existed in the periphery of dentistry since the 1930s. Through the development of sleep medicine research, dentists have gradually been able to contribute knowledge and skills in treating snoring and OSA patients. One of the first pioneers, Charles F. Samuels was inspired by his own snoring problems and developed a "tongue sleeve", designed to hold the tongue forward during sleep. The tongue device (TRD) increased the size of the oropharynx and also prevented mouth breathing (Cartwright & Samelson, 1982). One type of OA was created to treat mandibular retrognathy by pulling the mandible forward. It turned out that this treatment also had a secondary and positive effect on the upper respiratory tract. In 1983 an orthodontist called Peter George presented a patient with severe OSA where he had placed a modified activator to hold the mandible forward. This Mandibular Advancement Device (MAD) managed to reduce the patient's severe sleep apnea (Demko, 2018). The two scientists Soll and George published a letter in New England of Medicine (Soll & George, 1985) which brought the idea of MAD therapy for OSA to the American Medical Community.

Two types of OA with the same purpose, but different mechanisms exist. One type of MAD device holds the lower jaw in a protruded position, and the other type of OA is the TRD device which holds the tongue in a forward-facing position. Both devices have the intention to enlarge the volume of the upper airway.

In the years leading up to the 1990s, little research was performed with MAD therapy for SRBD. But from the turn of the century and onwards, more studies appeared with good quality and design. Gradually, MAD emerged as a treatment alternative for OSA treatment supplementing the CPAP. In the USA, an increasing number of MAD models received premarket approval from the Food and Drug Administration. In 1995 the American Academy of Sleep Medicine (AASM) published the first guidelines for treatment of OSA (Schmidt-Nowara et al. 1995). These guidelines were updated in 2015 (Ramar et al.,2015) These guidelines recommended MAD therapy for patients with mild and moderate OSA and those who are unable to use a CPAP.

The scientific support for the use of MAD has improved much in recent years (Table 2). In the period from 1950 to 1990, there were only 29 publications on PubMed that dealt with sleep apnea, snoring and MAD. During the next 10 years there were 221 publications and from 2001 to 2010 there were in total 515, and from 2011 and until 2020 a literature search yielded 868 publications with the same keywords on PubMed.

Table 2. *The development of scientific publications on PubMed from 1950 to 2020.*

Year	Period	No. of publications
1950 – 1990	40 years	29
1991 – 2000	10 years	221
2001 – 2010	10 years	515
2011 – 2020	10 years	868

A joint Health Technology Assessment (HTA) report from the Nordic countries in 2007 resulted in changes in clinical practice in Norway, where recommended treatment moved from surgery to CPAP and MAD therapy (Franklin, Rehnqvist, & Axelsson, 2007).

An overview of the clinical practice for OSA treatments showed a large discrepancy where in Sweden, 12,800 apnea devices were manufactured annually, whereas in Norway, only 12 apnea devices were customized in the same period. Treatment with the CPAP was at that time largely the same in the two countries (Franklin, Rehnqvist, & Axelsson, 2007).

1.6.3 Lifestyle interventions

Conservative (and reversible) treatment mainly consists of different types of lifestyle interventions, either alone or together with another type of treatment. Because obesity has become a growing problem globally, measures such as weight reduction, diets and physical exercise have become important factors in conservative treatment of sleep apnea. Smoking and alcohol both seem to aggravate OSA, and reduction or cessation of intake may contribute to reduction of OSA symptoms. Some allergies cause swollen mucous membranes and a narrowing in the airways in the nose and throat, and thus increasing OSA symptoms.

Sleeping positions may affect the severity of OSA, and a supine position in general, results in higher AHI (Eiseman, Westover, Ellenbogen, & Bianchi, 2012).

Information about the patient's sleeping position is important because a lateral position will reduce OSA symptoms and AHI severity in the majority of patients compared to the supine sleeping position. It is important to inform and educate OSA patients about sleeping position, as use of side-lying positions can reduce sleep apnea symptoms and severity (Srijithesh, Aghoram, Goel, & Dhanya, 2019).

One study from Australia tested a sleep position modification device aimed at making patients avoid the supine position. The position device used in this study was found to be effective in reducing supine sleep time and AHI as well, which was significant in those patients with baseline AHI ≥ 20 (Jackson et al., 2015). Another Australian study found that lateral positioning significantly improves the passive airway anatomy and collapsibility, and the ability of the airway to stiffen and contract and the awake functioning residual capacity (Joosten et al., 2015). However, even if positional therapy seemed to be an attractive treatment for some patients with OSA (Yingjuan, Siang, Leong Alvin, & Poh, 2020), the guidelines of the American Academy of Sleep

Medicine considered position therapy only as an alternative and additional treatment. But the new and recent technological advances have renewed the interest in positional therapy with the new inventions of devices.

1.7 MADs – considerations, procedure and therapy

1.7.1 Different types of MAD

There are many different MAD models on the market today. The first models were mono-blocks, i.e., the lower and upper jaw were connected in one part. The disadvantage with this type of device is that in order to titrate, a new, or a reconstructed device with greater protrusion has to be manufactured. However, the OAs used in our studies are custom-made and have a built-in adjustment option which means that the dentist does not have to make a new MAD to titrate. Most OAs used in Norway are individually tailored to each individual patient and consists of two parts: an upper jaw splint and a lower jaw splint. There is a large variation in design of the devices and their technical solutions. We mainly used individually and adjustable manufactured devices in the three studies (Fig. 11). In our opinion these models are of good quality, technically and functionally easy to use, and they have been used in several trials with satisfactory scientific support (Verburg et al., 2018).
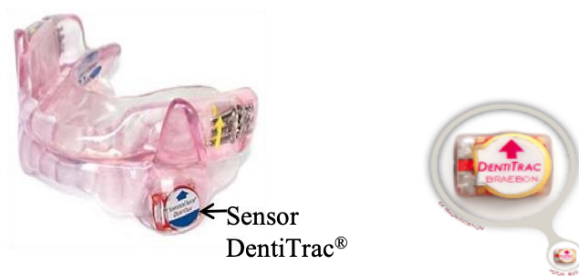
Fig. 11*. Somnodent device with a Dentitrac sensor.*

(By permission from SomnoMed)

The device can be made with different variations in design and functions. If the patient suffers from teeth grinding (bruxism), then the laboratory can reinforce the device. And if the patient has tendency to open the mouth during sleep, the laboratory can make fasteners for use of elastics. The device can be individually fitted to each patient, with attention paid to the anatomy of the patient teeth, the bite relations and the number of teeth in the mouth. The MAD is easy to adjust and titrate, and to do small corrections if the patient has got a new filling or a new crown by his dentist after the impression was taken. In addition, it is easy to relieve pressure points if needed on this type of MAD.

1.7.2 MAD procedure

The procedure consists of 1) the dentist takes impressions of each jaw, 2) an occlusal bite index is taken, and 3) the index and the impressions are sent to a certified dental laboratory (Fig.12). At the dental consultation a clinical examination of the teeth, intraoral conditions, and a functional evaluation of the masticatory system, including palpation of the temporomandibular joints and masticatory muscles are performed. The prerequisites for MAD treatment are the patient must have a satisfactory set of teeth in terms of tooth quality, number of teeth and location of the teeth. All teeth should be cleaned for oral pathological conditions and the patient should be treated if needed by his dentist. This means that planned fillings and / or prosthodontic treatment should be completed, before taking impressions for a MAD. The dentist measures the maximum protrusion, maximum opening capacity, lateral movements, any midline displacements and deviations of the mandible during protrusion. In our studies, George Gauge's bite registration fork is used as an aid to measure the horizontal and vertical relationship between upper and lower jaw. The baseline position of the MAD is usually registered in between 50% and 75% of maximum protrusion (Tegelberg et al. 2003).

Procedure at the *dentist*:
- Impression taken
- Bite registration with GeorgeGauge

Procedure at the *laboratorium*
- Making models
- Ready MAD
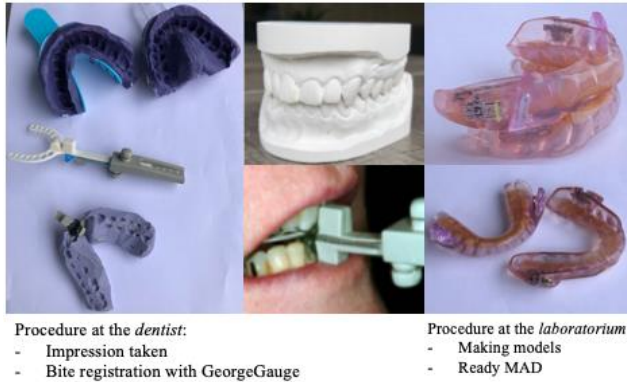
Fig. 12. *MAD manufacturing procedure. Photos: Kjersti Gjerde*

1.7.3 Mechanism of action

The mechanism of MAD has received much research attention, and it has been demonstrated that when wearing a MAD, the upper airway volume increased significantly (Marcussen et al., 2015). The MAD reduces the obstruction and facilitates free airways by protruding the lower jaw during sleep (Fig.13). The device should fit the patient exactly to get a good retention to the teeth. If it does not fit well, it will loosen, and the effect will be absent. When the patient has received the device, the dentist has to check fit and retention of the device, make sure it feels comfortable and is in the correct protruded position. It is important to have a check-up at the dentist repeatedly during the first half year, in order to be able to adjust the device to the optimal protruding position and possibly make other minor adjustments. Fit, function, protrusion and comfort are evaluated at the recall to achieve the best possible effect. At the 3-month check-up and if the subjective effect is satisfactory, the patient should be referred for a follow-up polygraphy (PG) to ensure the desired objective effect of the treatment. If we get a poor result with the new sleep measurement, several factors are checked to improve the result. We can increase the protrusion of the lower jaw, change the vertical position, check/improve the retention or switch to another type of device.
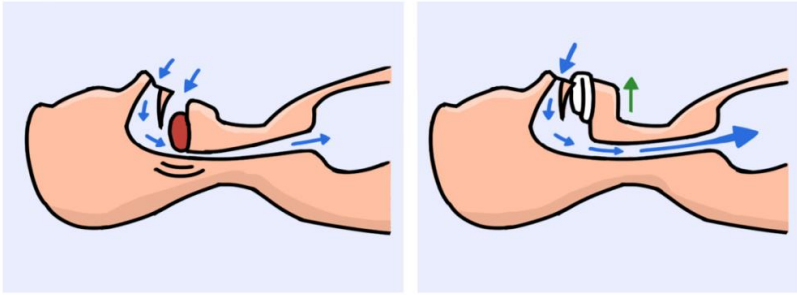
Fig. 13. *The mechanism of action of a device.*

(By permission from illustrator Thomas Madsen)

1.7.4 Indications for MAD treatment

The current indications for treatment with a MAD are patients suffering from mild and moderate OSA, "social snoring" or being non-compliant to CPAP therapy, and for patients who are not able to perform lifestyle changes. However, MAD can also be used in severe OSA when the patient does not tolerate, or is unable to use a CPAP. In addition, patients who travel a lot in connection with work can take an advantage of MAD treatment. In some cases, OA can be used in combination with a CPAP to reduce high pressure side effects, because the breathing machine will be able to work with lower pressure and thereby reduce adverse side-effects of CPAP. A recent Norwegian study reported that patients which requires maximum CPAP pressure and are diagnosed with severe OSA are expected to be non-responders to OA therapy (Storesund, Johansson, Bjorvatn, & Lehmann, 2018).

International Associations for Sleep Medicine in USA, Australia and Canada have provided recommendations for use of the oral appliance, and this is summed up in the table below (Table 3) (Johansson et al., 2014). No corresponding Norwegian guidelines exist in this area. However, a mini-health technology assessment report for the treatment of OSA was published at Helsebiblioteket in Norway in 2015 (Roth, Yknsøy, Aasen, Sunde, & Angeltveit, 2015).

Table 3. International guidelines for treatment with oral appliance.

Indications	Notes
Snoring	Effective against snoring, but robust data are missing on other health effects.
Mild to moderate sleep apnea	Non-compliant to CPAP, weight reduction and position therapy
Severe sleep apnea	CPAP treatment must have been performed without success

1.7.5 Contraindications to MAD treatment

MAD is contraindicated for patients suffering from central sleep apnea and other respiratory disorders than OSA. When the patient has acute jaw joint problems or suffers from severe periodontitis, MAD should not be offered to the patients before these symptoms are treated. Finally, with reduced opening capacity, i.e., <25mm, limited maximum protrusive distance (<6mm), active temporomandibular joint (TMD) disorder and inability to cooperate, or the skeleton is not fully developed, MAD treatment may be contra-indicated (Petit et al., 2002)

1.7.6 Side-effects of MAD treatment

The most common side-effects with MAD treatment are typically initial and transient. The initial side-effects are usually increased salivation and /or dry mouth, and tenderness and pain in teeth and in the jaw joints/muscles. Sometimes the patient feels that the bite does not fit in the morning, but this will usually disappear during the day, and is often experienced at the beginning of the treatment period. Chewing and jaw opening pains are common in the first few weeks. One study found low frequency of clinical signs of temporomandibular pain in patients with mild to severe OSA after 6 months of treatment with MAD (Nikolopoulou et al., 2020). In another study, minor side-effects were reported as relatively common, and led to termination of therapy in 1 out of 10 cases (Chen, Burger, Rietdijk-Smulders, & Smeenk, 2020).

More permanent side-effects are bite changes which are, for most people, trivial and minor. A recent study from Sweden concluded that between 2%–45% of the patients

report occlusal changes after 1 to 6 years of MAD therapy. But, less frequently they report any major and troublesome bite changes, even if all studies found significant reduction in overbite and overjet (Marklund, 2020) The repositioning with MAD consists in that the molar of the posterior part of the mandibula will move into a more class 3 relationship, and a changed inclination of the front teeth will decrease the overbite and the overjet (Marklund, 2020).

One of the main advantages with MAD is the reversibility, and the fact that MAD can be used as an alternative treatment for patient who are non-adherent to CPAP. Side-effects are generally small and the consequences of side effects must be balanced against the positive efficacy and the treatment outcome for snoring and OSA (Lindman & Bondemark, 2001).

2. Aims

The overall aim of this dissertation was to generate more knowledge about MAD as a treatment method for obstructive sleep apnea patients. The specific aims were to 1) evaluate a new measurement method for objective adherence of MAD, 2) to identify factors that can improve the adherence and the treatment effect of MAD, and 3) to quantify partners' influence and if their involvement could enhance these outcomes.

The objectives in each publication were:

Paper 1:

The first paper of the thesis was entitled: "Oral appliance treatment in moderate and severe obstructive sleep apnea patient non-adherent to CPAP". It aimed to evaluate the effect of individually adjusted mandibular advancement device in patients non-adherent to CPAP. In addition, it aimed to investigate whether there were factors which could predict treatment success or failure. The paper was published in *Journal of Oral Rehabilitation (Impact factor 3.9, Scientific Publication level 2 in Norway).*

Paper 2:

The second paper of the thesis was entitled: "Reliability of an adherence monitoring sensor embedded in an oral appliance for treatment of obstructive sleep apnea". The aim of this study was to test if digitally registered use of mandibular advancement device (MAD) with a built-in thermal sensor was reliable compared to self-reported diary of MAD use. The paper was published in *Journal of Oral Rehabilitation (Impact factor 3.9, Scientific Publication level 2 in Norway).*

Paper 3:

The third paper of the thesis was entitled: "Partner perception is associated with objective sensor measured adherence to oral appliance in OSA". The two aims of this study were to determine objective sensor measured adherence to MAD therapy and to assess if a bedpartner might have an impact on MAD adherence. This paper is published in *Journal of Sleep Research (Impact factor 3.8, Scientific Publication level 1 in Norway).*

3.   Material and methods

This dissertation was planned, developed and performed in a specialist-clinic at the Center of Sleep Medicine at Haukeland University Hospital, Bergen.

This Phd was conducted in my scholarship period between 2017 and 2021.

3.1 Study 1

3.1.1 Design
This study design is a retrospective, longitudinal patient-series study design.

3.1.2 Settings, participants and data collection
The data collection was retrospectively done in the period from 2007 until 2013 in patients (n =116) non-compliant to CPAP that were referred to a dental specialist clinic localized at the Center of Sleep Medicine at Haukeland University Hospital, Bergen for follow-up after MAD treatment. Ten patients were missing at the follow up and the total final data material contained 71 men and 35 women (n=106). Both baseline and follow-up examinations were done by respiratory medicine or ENT specialists, and scoring criteria used were in accordance with the 2007 AASM manual (Ito & Inoue, 2015).

3.1.3 Inclusion criteria
- All genders with moderate and severe OSA
- Patients non-adherent to CPAP
- Baseline sleep study before OA treatment
- Follow-up sleep study using the OA

3.1.4 Exclusion criteria
- Central sleep apnea
- Periodontal disease of severe grade
- Too few teeth to anchor an OA device
- Acute TMD

3.1.5 Outcome measure

Change in AHI.

Success criteria were divided into four levels based on polygraphy at follow up:

1) AHI<5

2) 5 ≥AHI ≤10 and 50% reduction from baseline

3) AHI≥ 50% reduction in baseline AHI

4) AHI<50% reduction in baseline AHI (failure)

3.1.6 Oral appliance treatment

Impressions of the mandible and maxilla were made, and a George Gauge index was taken in the range of 50–80% of max protrusive capacity. All the appliances were custom-made and mostly all was dual-block adjustable design. After 4–8 weeks the patient got a new appointment for adjustment and titration.

3.1.7 Statistical analyses

Due to lack of normality in the data distribution, the non-parametric Mann-Whitney U-test was used to calculate the difference between the moderate and severe OSA groups and between the treatment outcome groups (success/failure).

Regarding AHI, ODI and oxygen-saturation parameters the Wilcoxon signed rank test to analyze the intra-individual differences between baseline and follow up was used.

Logistic regression analysis with the strictest success criteria for the dependent variable at follow-up, i.e., success AHI < 5 vs. failure: AHI ≥ 5 were used. The independent variables were dichotomized. Regression analysis with unadjusted and adjusted odds ratios was calculated.

3.2 Study 2

3.2.1 Design

Paper 2 is a reliability study design where we calculated the relative and absolute reliability of the MAD sensor compared to self-reported sleep time. The purpose of this

study was to test if digitally collected data on MAD use where as reliable as self-reported MAD use.

3.2.2 Setting, participants and data collection

In this reliability study we included patients with all grades of OSA, and all study patients were non-adherent to CPAP. The total data material included 80 patients, both men and woman were participating, and the age-range was between 25 and 75 years. All the study patients were recruited from the Center of Sleep Medicine at Haukeland University Hospital in Bergen.

3.2.3 Inclusion criteria

- Adults 25–75 years and both genders
- All severity grades of OSA; mild, moderate and severe grade.
- All participants had to participate in a clinical baseline examination
- Non-adherent to CPAP therapy after 3 months use

3.2.4 Exclusion criteria

- Central sleep apnea
- Periodontal disease of severe grade
- Too few teeth to anchor an OA device
- Acute TMD

3.2.5 Outcome measures

We measured self-reported and sensor-reported use of MAD in hours during sleep for a period of 30 consecutive nights. The self-report was done by using a diary where the patient reported numbers of hours in use every night. The sensor-reported use was retrieved by placing the sensor in a docking station and retrieving data from a specially designed software for the sensor (Fig.14). Of totally 2400 nights of measuring, we were able to retrieve data for 2108 nights. Missing data were few and mainly caused by lack of data in self-reported diaries.

The thermal sensor is embedded in the MAD. The equipment used for readout is shown in the picture below. The base-station is connected to the PC and the software and the result from the read-out shows on the screen, which is illustrated below. The built-in

sensor measures hours and minutes of MAD use during every night. The sensor recording demonstrates the month and date, total usage time and time in supine and non-supine position. Data can be stored for 6 months, and the battery capacity is 5 years.
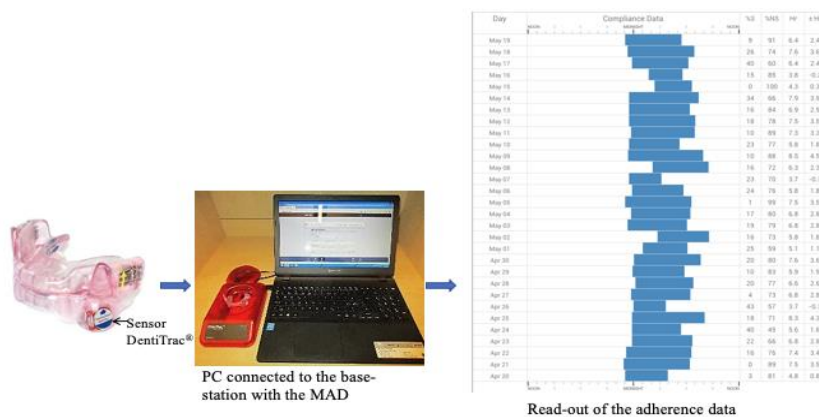
Fig. 14. Equipment used for objectively readout of adherence
(Photo: Kjersti Gjerde)

3.2.6 Statistical analysis

To determine the relative reliability of the OA sensor, a correlation analysis was performed.

We used a correlation plot containing the pairwise plots of self-reported MAD usage time in a Bland-Altman plot with 95% limits of agreement between self-reported and digitally registered time. We decided to use the intraclass correlation coefficient ($ICC_{3,1}$), which is a correlation analysis with a two-way mixed effects model accommodating consistency from a pairwise measurement.

The absolute reliability is a measure of reliability related to the scale in question. In this situation time, in a digital conversion was assessed using mean S_w: (Mean difference*1.96 ±SD).

3.3 Study 3

3.3.1 Design

Paper 3 was a prospective, longitudinal case-series study design.

3.3.2 Settings, participants and data collection

During a period of 10 months 82 consecutive patients were recruited from the waiting-list from the Centre for Sleep Medicine at Haukeland University Hospital in Bergen. Totally 77 patients became participants: 52 men and 25 women. Out of 77 participants 57 were married or living together and 20 were single. Both patients and partners signed an informed consent before the study started. Adherence and treatment outcome were determined at the final follow-up.

The Type of MAD used in this study was a Somnodent Fusion™ with an embedded sensor from Dentitrac™.

3.3.3 Inclusion criteria

- Adults 20 years and both genders

- All severity grades of OSA; mild, moderate and severe grade.

- All participants were subject to a clinical baseline examination before entering the study

- Non-adherent to CPAP therapy after 3 months use

3.3.4 Exclusion criteria

- Central sleep apnea

- Periodontal disease of severe grade

- Too few teeth to anchor an OA device

- Acute TMD

3.3.5 Outcome measures

- Treatment effect of MAD was measured as the change in AHI from baseline to follow-up in polygraphy measurements

- Objectively measured adherence by means of an embedded chip in the MAD

- Sensor measured adherence in relation to treatment effect

- Partners' influence on adherence was assessed by using a questionnaire to patients and bedpartners

3.3.6 Statistical analysis

We performed a sample size calculation of the statistical power needed before study start. We expected group (patients and bed partners) to be a strong predictor in the regression model. If this predictor alone explained 10% (R^2=0.1) of the total variance in total time of adherence, then 73 persons were needed to obtain statistical differences (using a 0.05 level of significance and a power of 0.8). If three variables (patient group, daytime sleepiness, and psychosocial factors) explained 15% (R^2=0.15) of the total variance in total time of adherence, then 66 persons were needed. Bearing possible drop-outs and additional random variation in mind we reckoned that 80 persons were needed in the study. Descriptive statistics for statistical group differences were performed with parametric Student paired *T*-test, when the data were normally distributed, and the non-parametric Wilcoxon/Mann-Whitney for paired comparisons of between group differences, respectively.

Sensor-recorded adherence was dichotomized before the analysis in two ways: (1) Good adherence was weekly use of the MAD for ≥ 4 hours/night and ≥5 out of 7 days and if the appliance was worn equal to or more than 70% of the monitored weeks; (2) Alternative good adherence was if the patients used the appliance ≥ 4 hours/night and ≥70% of all nights. Below 70% of the weeks/nights was labeled as poor adherence in both adherence categories. A multivariate analysis with logistic regression analysis was performed with adherence (as per no. 2 above) as the dependent variable. In the adjusted model, independent variables were those found to be significantly correlated to adherence in the unadjusted analyses.

Table 4. Summary of statistical tests and methods in the three papers.

Statistical tests/methods	Paper 1	Paper 2	Paper 3
Mann Whitney U test	X		X
Wilcoxon sign rank test	X		X
Pairwise Bland Altman plot with 95% limits for agreement		X	
Relative reliability: Intraclass correlation coefficient ($ICC_{3,1}$),		X	
Absolute reliability: Mean S_w: (Mean difference *1.96 $\pm SD$)		X	
Students paired *T*-test			X
Adjusted/unadjusted multivariate logistic regression	X		X
Spearman Rank Correlation (Spearman's Rho)	X		

3.4 Ethics

The World Medical Association has developed the Declaration of Helsinki (World, 2013). This declaration is a statement of ethical principles for medical research involving humans.

Participation in the studies was voluntary and based on a written informed consent before the trial period started. All participants were allowed to withdraw from the studies without giving any reason and without resulting in any negative impact for the individuals. All data collected were anonymized by a code and kept safely locked and secured.

The study protocols were reviewed and accepted by The Regional Committees for Medical Research Ethics (REK Vest), Norway. (Study 1: protocol no. 2009/1229, Study 2: protocol no 2014/1613, Study 3: protocol no. 2018/1771). Study 1 and 2 was by the ethical committee deemed to fall under quality assurance projects and did not need to be handled by the committee, while Study 3 was formally assessed and approved by the ethical committee.

4. Summary of results

4.1 Paper 1: "Oral appliance treatment in moderate and severe obstructive sleep apnea patients non-adherent to CPAP"

This paper reported:

- The treatment success rate for the group with moderate OSA was 77% and for the group with severe OSA 69%, based on success-criterion 3 ($\geq$50% reduction in baseline AHI). For the whole group the total success rate was 75% according to criterion 3.

- We found no significant difference in the treatment-outcomes between the moderate and the severe group.

- In the bivariate analysis between treatment outcome and baseline parameters, the two success groups had a lower prevalence of cardiovascular disease ($p<0.05$), and lower age and BMI.

- In the final regression model, $SpO2_{nadir}$ was the only factor that had a significant predictive value for failure or success for treatment with MAD.

4.2 Paper 2: "Reliability of an adherence monitoring sensor embedded in an oral appliance used for treatment of obstructive sleep apnea"

This paper reported:

- Mean self-reported time with MAD use was 6.87 hours

- Mean DentiTrac time with MAD use was 7.06 hours

- The absolute reliability, expressed as the difference in means between the two measurement-methods was 10.2 minutes.

- The intraclass correlation coefficient (ICC) was calculated to: $r = 0.847$ which indicated a high relative reliability.

4.3 **Paper 3:** "Partner perceptions are associated with objective sensor-measured adherence to oral appliance therapy in obstructive sleep apnea".

This paper reported:

- MAD adherence could be measured objectively with the built-sensor for a mean period of 8.3 months.

- Adherence based on device worn $\geq$ 4 hours per night, $\geq$ 5 days a week was 60.1%.

- Treatment outcome (change in AHI/ODI) was positively correlated to the degree of MAD adherence.

- Partner perception of snoring and apneas during the night was positively associated with adherence.

5. Discussion

5.1 Methodological considerations

5.1.1 Research methodology and validity

Several scientific study designs have been developed in order to minimize bias and generate robust data and new knowledge. It is important to choose trial designs that are suitable for generating valid answers to the research question. In this PhD project I have decided to only use quantitative data as results. In particular, partner questions about factors affecting adherence, could potentially broaden our understanding of how human interaction may interfere with the treatment outcome.

Good correlation has been found between results in randomized controlled trials and large studies with an observational study design. Prospective designs and large sample size are factors that can improve the validity of non-randomized studies (Ioannidis, Haidich, & Lau, 2001).

5.1.2 Internal validity

Internal validity has to do with the methodological quality of trials, study protocol and trial design. Statistical analyses for differences and correlations can both be checked for internal validity and evidence-graded according to internal validity checklists like the Oxford Levels of Evidence (CEBM, 2009).

In the three studies we took measures for missing data to minimize selection bias. During the observation periods of 12 (Paper 1), 1 (Paper 2), and 8 months (Paper 3), respectively, we managed to keep the amount of missing data below 10%. We attribute this to effective follow-up routines by telephone contact with the patients between appointments.

Several systems have been developed to rank trial quality and the possible risk of bias: use of control group, use of randomization, concealed allocation to groups, blinding procedures and loss of data due to withdrawals or drop-out. These criteria can be used to evaluate the internal validity of a study, and it is commonly considered that studies

with control groups have higher internal validity than observational studies with analysis of odds ratios (Ioannidis et al., 2001) (Janiaud et al., 2021).

RCTs are time-consuming and require manpower to perform. Randomization procedures, concealed allocation to groups, all require multiple persons involved in the performance of the study. Our limited resources for the project did not allow us to perform a full RCT. The prospective design used in the third study is methodologically stronger than the retrospective design in the first study (Ioannidis et al., 2001).

We explored the RCT literature about placebo devices to MAD, and were not convinced that measuring against heterogeneous types of placebo would be valid. We found a recent meta-analysis with CPAP and MAD (Schwartz, Acosta, Hung, Padilla, & Enciso, 2018), but only one study comparison of MAD was done versus a placebo MAD (Aarab, Lobbezoo, Hamburger, & Naeije, 2011). The near-identical placebos mostly consisted of either the lower, or upper part of the dual block MAD. In one RCT, the placebo MAD was a monoblock without protrusion (Petri, Svanholt, Solow, Wildschiødtz, & Winkel, 2008). The variation in appearance and function for the placebo intervention may pose a validity problem. The majority of placebo controls had no significant effect on AHI (Mehta, Qian, Petocz, Darendeliler, & Cistulli, 2001) (Johnston, Gleadhill, Cinnamond, Gabbey, & Burden, 2002). But in one study, the intra-oral placebo device showed a worsening of AHI values from baseline (Dal-Fabbro et al., 2014), while another trial showed a significant improvement in AHI (Aarab et al., 2011). The mean difference in AHI between the two types of devices was 11.9. This fairly large difference in change of AHI may threaten the validity and suggests that using intra-oral placebo devices is volatile and maybe not as precise and homogeneous as comparators should be. In another study, the placebo device caused a mean increase in AHI by 10.6 (Duran-Cantolla et al., 2015). Consequently, we decided that comparing baseline values with follow-up values seemed clinically relevant, although maybe not as valid as comparing MAD versus a placebo group.

Another issue was to reduce drop-outs and withdrawals. This was solved by keeping a tight connection to patients while they were in the observation period.

It is important to have a robust protocol, use valid and reliable measurement tools in research. This ensures stability and all participants are measured in the same way. Changes in diagnostic criteria for OSA over time may confound the precision of results. The diagnostic threshold for scoring a hypopnea was changed after 2012, from 4% of O_2 desaturation to 3%. (Berry et al., 2012). But in our clinic the 3% threshold was not implemented before 2019. It is important to note that, in Study 1 and Study 2, the old threshold value of 4% SpO_2 was used, while 3% SpO_2 was used in Study 3.

In prevalence studies of OSA, reviewers have to be aware that the material may consist of different SpO_2 threshold values. The threshold value was reduced from 4% to 3 % by the research societies during the last decade. Some reviews have solved the problem by splitting the material for each threshold value in separate calculations (Senaratna et al., 2017).

Another area of discussions in the OSA treatments literature are the various criteria for successful treatment. It is always a challenge to dichotomize continuous effect data in a valid way. In Study 1, we adopted four commonly used levels for the success/failure outcomes (Table 5).

Table 5. *Success criteria used in Study 1.*

Success criterion	AHI at follow-up	Verdict
1	AHI< 5	Success 1
2	<5 AHI< 10 and more than 50% reduction in baseline AHI	Success 2
3	>50% reduction in baseline AHI	Success 3
4	<50% reduction in baseline AHI	Failure

Moving from successful effect data to adherence data, we also experience some challenges. The adherence criteria used in Study 3 was found in the OSA literature on CPAP adherence, and the adherence data are based on the number of nights MAD was in use. But to count as a night of adherence, MAD had to be in use for at least 4 hours per night. The data were dichotomized into number of adherence nights, and then summed up. Our continuous data showed that; when worn, MAD was used on average 6.4 hours per night.

5.1.3 External validity

Validity is often divided in two: (1) internal validity which is described above, and (2) external validity. The latter has to do with how the experimental situation and included material, reflects clinical practice and whether the findings can be generalized to "real-world" patients. Our patient sample was drawn from patients at a specialty sleep clinic. Recent research has broadened the understanding that co-morbidities are highly prevalent in OSA-patients, and that their general health status may be poorer than the average population. This may have a confounding negative influence on the effect size of treatments, as few patients with severe OSA had been included in early studies with MAD. The patient samples in the three studies were limited to patients non-adherent to CPAP, and it may be questioned whether this has had an influence on the effect size and the external validity.

5.1.4 Reliability

Reliability, repeatability and reproducibility are important concepts to examine a measurement method or test's ability to reproduce precise and consistent results. A measurement method is considered reliable if it produces the same results every time. We distinguish between the absolute and the relative reliability (Kubala et al., 2020) In my second study reliability was measured as relative reliability using Intraclass Correlation Coefficient (ICC) two-way random model 2,1. We interpreted the relative reliability estimates, that is, ICC values of ≥ 0.7 and ≥ 0.9 represent good and very good reliability, respectively. Absolute reliability was calculated in minutes and inspected using Bland-Altman plots (Bland & Altman, 1996) (Giavarina, 2015).

5.1.5 Statistical methods

In Study 1, no power analysis was performed for sample size calculation. In the second study a convenience sample of $n=80$ was used, since there is a consensus that this is sufficient to get robust data in reliability studies. In the third study a power analysis for the estimation of the required sample size was performed.

Correlational studies have their strengths in quantifying risks and relationship often tested by odds ratios and a number of factors that might affect risk ratios. This is useful when investigating incidence and prevalence of disease, or development of the natural course of disease. In the first study, statistical correlational methods like multiple regression analysis were used to find out if any factors could predict treatment failure and success. This regression analysis revealed that $SpO2_{nadir}$ was the only factor that had a significant predictive value for failure or success for treatment with MAD.

In Study 3 logistic regression analysis of correlation was used, to reveal that partners' interrupted sleep from snoring and breathing stops, was positively related to MAD adherence. Likewise, methods like Mann-Whitney U-test and Student t-test to seek for potential statistical differences between the different OSA severity categories and between adherence groups and treatment effects was used.

5.1.6 Discussion of the methodology in Study 1

In Study 1, previously registered patient data with a retrospective patient-series study design was used. A strength of this study was the fairly large sample size ($n=106$ per protocol) and that only a few patients were lost to follow-up (8.6%). A weakness of the study is the retrospective design. Similarly, the study was performed without a control group, which could have provided data on the natural course of the disease and treatment progression.

5.1.7 Discussion of the methodology in Study 2

In Study 2, a standard design to test reliability of the embedded chip in sleep time recording was used. The sample size $n=80$ was determined by the convention that > $n=50$ gives robust data in reliability studies. The study design enabled determination of both the relative and absolute reliability of the chip and made possible a comparison

with the current standard: patient-registered sleep time, by self-reported diary. The relative reliability of the embedded sensor was satisfactory, and the absolute reliability was only 10 minutes apart from self-registering. The weaknesses of the study were the lack of a high precision gold standard for comparison. Subjective registering is often imprecise as patients often forget to register sleeping time or make a less accurate retrospective recollection of their sleep time. To improve the precision in this study, the optimal comparison would probably be to compare the chip data with data from a simultaneous sleep laboratory test.

5.1.8 Discussion of methodology in Study 3

In the third study, the same study design as in Study 1 was used, but with the improvement by using a prospective design rather than a retrospective design for the data collection. We incorporated an *a priori* sample size calculation in order to have sufficient statistical power to obtain robust results. The polygraphy data for each patient were computer-generated and afforded no possibility for the observer to interfere with the PG results. Another strength of the study was that only 6.1% of patients were lost to follow-up, in spite of a fairly long treatment period of 8 months.

One of the more challenging parts of the project, was to design a questionnaire that could capture the partner perceptions of MAD use in OSA patients. We could not find an appropriate standardized and validated questionnaire, and we had to rely on the clinical experience of the author team to develop this. In hindsight, we saw that some of the questions concerning the partner relationship may have been too sensitive or intimate to answer truthfully. Clearly, more work is needed to refine the questionnaire and to validate it. Still, we reckon that the findings are reasonably valid for the importance of patient and partner support as the partner's snoring and apneas turned out to be the most important predictor for good adherence.

5.2 Discussion of the clinical results

5.2.1 Paper 1

In this paper, the effect of the individually adjusted mandibular advancement device (MAD) was tested in patients with moderate and severe OSA. The overall success rate

was 75%. Our starting point for developing the current project was that our clinical experience suggested that not only moderate, but even severe OSA patients could have a relevant effect of the MAD. However, MAD has not been recommended for the severe category of OSA in the AASM guidelines of 2006 (Kushida et al., 2006). Clinical practice adhered to this in Norway at the time of planning and seeking funding for our project. This notion was backed by a study which concluded that MAD was not effective for severe cases (Johnston et al., 2002). A recommendation of MAD was given in more recent literature (Ramar et al., 2015). Our findings in study 1 supported that MAD treatment of severe OSA, may be relevant in cases where other treatment options like CPAP and lifestyle interventions have failed. Although the success rate in Study 1 was a little smaller in the severe group, the difference between severe and moderate groups was non-significant.

Another question is why a PG test with MAD is necessary? In this study one in five patients, improved AHI after MAD treatment, but did not fulfill the success criterion of more than 50% reduction from baseline AHI. Another important point showing the need for PG, is that seven patients in the failure group actually worsened their AHI by 5–10 AHI units during MAD treatment. In a "no harms" perspective, it may be important to perform a PG to protect the patients from getting worse from treatment. The clinical relevance of a reduction in AHI down to 5–10 should be considered against baseline AHI-values, and other possible benefits from MAD.

In Paper 1 we identified one possible factor of importance for predicting treatment success or failure for MAD therapy. The result of the regression analysis showed that baseline SpO2 nadir was the only factor that had a significant predictive value. The take home message of this finding is that patients with a low SpO2 nadir may not achieve an acceptable treatment result with MAD. But this should not alone determine whether patients should have a MAD or not, but it should be considered together with the individual PG results. And this finding must be explored in future studies.

Researchers both in medicine and dentistry have been searching for predictors of success for MAD therapy. Imaging was used to try to uncover a narrow upper airway (UA) or anatomic constrictions to make the site of obstructions visible (Lowe, Ozbek,

Miyamoto, Pae, & Fleetham, 1997) (Lowe et al., 1996) Some controlled studies have found that gender, and body position during sleep were evident. The site of obstruction was found to be important for MAD success because airway size varies with patient's position and plays a role in airway collapsibility (Ishida et al., 1998) (Chung et al., 2010) (Lee, Paek, Chung, & Kim, 2017).

A high CPAP pressure has been considered to give decreased effectiveness of MAD (Marklund & Franklin, 1996) (Storesund et al., 2018).

All the abovementioned factors could play a role in determining which patients will become responders to MAD. It is important to investigate further if we can separate suitable from non-suitable MAD patients.

5.2.2 Paper 2

Long-term adherence to treatments in OSA is crucial for the clinical outcome. Measuring adherence objectively is important, as we need measurement methods which are not vulnerable for human errors, but can provide accurate data on hours in use per night.

The aim of Paper 2 was to test if use of MAD with a built-in sensor was a reliable procedure compared to a self-reported diary of MAD use. The reason why we wanted to test this, was to determine the reliability of a potentially objective measuring method to register adherence to MAD use. For decades CPAP machines have incorporated a sensor and timer to objectively measure adherence. For MAD, (Dieltjens et al., 2013), such sensor has existed for some time, but they have not been in standard use like the CPAP timers in the clinics (Xu et al., 2021) (Dieltjens et al., 2013). MAD sensors are becoming more common as technology advances and data storage capacity increases.

It was interesting to see that the sensor was technically reliable in the sense that we only found technical failures in 0.2% of the patient data. The most common reason for missing data in self-reported data was patients forgetting to report time in use. The mean self-reported MAD use was 6.87 hours, and the mean sensor-reported MAD use was 7.06 hours. In other words, the absolute reliability, expressed as the difference in means between the two measurements methods was 10.2 minutes. ICC was high at

0.855, which indicate a good, to very good correlation. We conclude that the sensor provides reliable data on adherence for one month.

A disadvantage with retrospective self-reporting is that errors may occur. Sensor-reporting on the other hand cannot be manipulated. Maybe the most precise way to report MAD usage time is to test this in a sleep laboratory. This is, however, too time-consuming and expensive to implement on a standard basis.

Another added feature of the sensor is that it can register the patient's body-position, i.e. supine and non-supine. This might provide useful information about position-related OSA. But this was outside the scope of the current study.

5.2.3 Paper 3

There were two aims in this paper. The first aim was to determine objective, sensor-measured long-term adherence to MAD in relation to treatment outcome. And the second aim was to investigate if bedpartners attitude and support might have an impact on MAD adherence. We found that MAD adherence could be measured objectively with a built-in sensor for an average period of 8.3 months, and that good adherence was positively related to PG-measured results. The mean adherence to MAD depended on the various success criteria, but was measured to about 60% per week (based on the criteria normally used to measure CPAP adherence), and when in use, the MAD measured on average 6.4 hours of use per night.

Another important result was that treatment outcome was positively correlated to the good adherence group. The AHI improvement was significantly higher at an average of 17.4 in the good adherence group compared to 11.0 in the poor adherence group.

Partner's perception of snoring and apneas during the night was positively associated with good adherence. More than half of the patients considered partner support to be important for their adherence to MAD.

In the good adherence group two out of three bedpartners reported that MAD use had a positive impact on their marital relationship. From a patient perspective, half of patients with good adherence reported that MAD use had a positive effect on sharing the bedroom.

Partners' attitude and support may be a resource that should be further exploited to improve MAD adherence. For CPAP, it has been shown that behavioral and supportive interventions can yield a significant effect on CPAP usage (Askland et al., 2020).

We have pointed out in this study, that adherence is important for the outcome of MAD therapy. Other studies have found that self-reported adherence is higher in adjustable devices, and another study found that adherence correlated with the length of the mandible (Bachour et al., 2016) (Attali et al., 2016) (Ingman, Arte, Bachour, Bäck, & Mäkitie, 2013). Johal et al. pointed out in their study that OA treatment is completely patient-dependent, and that patient comfort and adherence is decisive for success. (Johal, Haria, Manek, Joury, & Riha, 2017).

5.3 General discussion and clinical considerations

This thesis consists of three papers. MAD was used in all three studies as a treatment of OSA. In both Study 1 and Study 3, the treatment effect was an important outcome-measure, and in Study 2 objective sensor-measured MAD adherence was the primary outcome measure. In Study 3, factors influencing MAD adherence were introduced, by bringing the partner perspective and partner interaction forward.

The overall aim in the thesis was to investigate adherence and identify factors associated with treatment outcome for MAD therapy in order to get the best possible treatment result. Regarding study design, the thesis evolved and improved in terms of scientific quality during the project. In real life, it is often limitations in terms of personnel resources, funding, available research infrastructure and patient material. In this perspective, the project seems to have been fairly successful within our limitations and the framework of what was practically possible.

The results presented in the dissertation confirm that the mandibular advancement device is a viable option in treatment of OSA. Our studies show that MAD is capable of decreasing AHI and reducing snoring. Although our case series design limits firm conclusions on effect, both Study 1 and Study 3 found fairly large effect sizes, which suggests that the evidence for a positive effect of MAD is consistent and valid. Even for patients suffering from severe OSA, MAD can reduce AHI with clinically relevant

effects. An additional advantage with MAD is its smaller size and easier to bring than a CPAP device.

The adherence rate to MAD in Study 3 was 60.1%, which was in line with or a little lower than recent studies using objective measurements (Xu et al., 2021) (Pahkala & Suominen, 2021). The patients in the latter studies had not tried CPAP before MAD therapy. If we summarize predictive factors for MAD failure in our studies, then SpO_2 nadir was the only factor that could firmly predict MAD failure. Other authors have pointed out that in mild OSA at baseline, problems with MAD use in the first few months predicted poor long-term results. Additionally, prior use of CPAP was predictive for MAD failure after 5 years (Vecchierini et al., 2021). It may be speculated that patients who have proved non-adherent to CPAP, might have had poorer adherence to MAD than patients who have not tried CPAP before. This may explain why the other studies sometimes had better results. A recent study of long-term use of MAD, supports this assumption (Vecchierini et al., 2021). The new insight may have clinical consequences and could potentially be a confounder for comparisons of effect between different treatments.

In the thesis we found that treatment outcome was positively correlated to the degree of MAD adherence. To measure adherence, we used a thermal sensor which we tested and found highly reliable. The sensor objectively measured adherence which gives us new possibilities to directly compare MAD adherence with CPAP adherence. The CPAP is routinely equipped with a sensor for measuring adherence which now also can be done with the MAD.

The thesis reveals that adherence is important for treatment outcome, and that partners' attitude and support may be a resource that could improve adherence. From the partners' perspective the MAD use had a positive impact on the relationship and on sharing the bedroom. We performed a literature search for relevant questionnaires, but failed to find any. In this perspective, we decided to develop our own questionnaire where both OSA patients and their bedpartners were questioned at baseline, and at 3 and 6 months of MAD treatment. In order to keep the questionnaire as short as possible, only a few questions about bedroom sharing were included. However, there is support

in the literature to assume that the importance of support from the partner is dependent on the quality of the partner relationship, i.e., it is mainly important if the partner relationship is close and warm (Coan, Schaefer, & Davidson, 2006).

Thus, if questions of relationship satisfaction had been added, these could have moderated the weak association observed between partner support and treatment adherence and treatment effect.

Another issue for improvement was the lack of a standardized procedure for how the participants should complete the questionnaire, ensuring that patient and partner answered the questionnaire separately. It is reasonable to expect that at least some of the couples may have completed the questionnaire in cooperation, and therefore the answers from the patients and his or her bedpartners may not reflect their independent opinions. This could have influenced the observed associations between partner support and treatment adherence and treatment effect.

6.   Conclusions

This thesis contributes with new knowledge in the field of treating sleep apnea patients with a mandibular advancement device and the clinical challenge related to factors affecting treatment outcome and the importance of adherence to MAD.

In line with the specific aims of the thesis, the following main conclusions could be drawn from the results:

Paper 1 revealed the treatment effect of mandibular advancement device in patients non-adherent to CPAP, to be similar in the moderate and the severe patient groups. There was no significant difference between the treatment success rate between the two groups. This result may indicate that MAD could be a good alternative in treatment of obstructive sleep apnea also in the severe group in sleep clinics with skilled dentist and repeated follow-ups during the initial treatment period. This paper also revealed that SpO2 nadir was the only factor that had a predictive value in the regression analysis. This can indicate that low SpO2 in baseline PG may result in failure regarding MAD treatment. However, these results should be reproduced in an RCT study before firm conclusions can be drawn.

Paper 2 showed that digitally registered use of MAD with a built-in sensor was reliable compared to self-reported diary of MAD use. This finding is important because we can measure adherence to MAD objectively in clinical practice and do not have to trust only self-reporting MAD use.

Paper 3 revealed that MAD adherence could be measured objectively with the built-in sensor for a period of more than 8 months. This study also showed that treatment outcome, measured as change in AHI and ODI, was positively correlated to the degree of MAD adherence. In addition, this paper found that partners' perceptions of snoring and apneas during the night are positively associated with adherence. These findings confirm that partners' attitude and support may be a resource that could help to improve MAD adherence.

7. Implications and future perspectives

This research project has brought us new knowledge about MAD and factors that are important for optimal benefit of MAD treatment. Adherence is interesting to investigate because lack of adherence can reduce benefit from the treatment. Poor adherence is a problem that may result in lower effect size for most OSA interventions. Consequently, there is a need for optimizing several OSA treatment options.

At the start of this project, we were in doubt whether the placebo MADs really are inert, or if they might have a positive or negative effect. However, it seems that most of the recent studies used one part of a MAD for placebo, and this placebo did not induce any significant difference in change from baseline. There is still a need to compare other interventions with MAD in controlled studies. This could help us define more exactly what the true efficacy of MAD is. In particular, it could be interesting to perform a placebo-controlled study with MAD in patients with severe OSA, all though there are several ethical challenges concerning such study design.

The broad variation in dichotomized success outcomes in the OSA literature is a challenge. In Study 1, four different success criteria were used. It would be easier to compare if success criteria were fewer and more homogeneous. And one might consider more use of continuous data, rather than dichotomized data with rigid cut-off thresholds.

Another issue for future studies is to make more valid comparisons of treatments for obstructive sleep apnea. Some of the previous comparative studies may have been confounded by a patient selection bias, as prior non-adherent use of CPAP recently has been found to be associated with a negative prognosis for MAD adherence. This may also explain why our material of non-adherent CPAP patients scored slightly lower MAD adherence than other studies without such a patient selection bias.

In the future it is important to explore more about the interactions between patients and partners. We should investigate the construct validity of the questionnaire and test its reliability. Qualitative interviews could probably shed more light on motivation and barriers in both groups.

8.   References

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Original Papers I, II and III

Paper I

Oral appliance treatment in moderate and severe obstructive sleep apnoea patients non-adherent to CPAP

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SUMMARY The aim of this retrospective study was to evaluate the effect of individually adjusted custom-made mandibular advancement device/oral appliance (OA) in treatment of patients with moderate and severe obstructive sleep apnoea (OSA), who were non-adherent to continuous positive airway pressure (CPAP) therapy. During 2007-2013, 116 patients with moderate ($n = 82$) and severe ($n = 34$) OSA non-adherent to CPAP treatment were referred for dental management with an individually adjusted OA at a specialist sleep clinic. Ten of the participants (8·6%) were lost to follow-up, leaving the data set to consist of 106 patients (71 men/35 women, mean age 57 year, range 28-90). Nocturnal respiratory polygraphic recordings were performed at baseline and follow-up. Average time between baseline polygraphy and follow-up was 12 months. A successful OA treatment outcome was based on polygraphy at the follow-up and divided into three groups: 1 = AHI <5; 2 = 5 ≤ AHI <10 and >50% reduction in baseline AHI; and 3. >50% reduction in baseline AHI. If there was a ≤ 50% reduction in baseline AHI at the follow-up, the treatment was considered as a failure. The overall treatment success rate was 75%. There was no significant difference in success rates between patients in the moderate and severe categories (69% and 77%, respectively). Low oxygen saturation (SpO_2 nadir) had a high predictive value for OA treatment failure. OA treatment of patients non-adherent to CPAP is efficient and especially promising for the severe OSA group who are at greatest risks for developing serious comorbidities, if left untreated.

KEYWORDS: continuous positive airway pressure, mandibular advancement, medical device, obstructive sleep apnoea, oximetry, somnography

Accepted for publication 17 November 2015

Introduction

Obstructive sleep apnoea (OSA) is a common disorder, although prevalence varies widely in the literature. When using strict diagnostic criteria (full, attended nocturnal polysomnography), a recent systematic review reported prevalence among community-screened adult patients to range from 2% to 14%. The prevalence varied depending on the cut-off value of apnoea hypopnoea index (AHI), and for ≥5 events h^{-1} and ≥15/h, the prevalence was 14% and 6%, respectively (1). Similar frequencies have been found in a large Norwegian population-based study where the estimated prevalence of OSA was 16% for AHI ≥ 5 and 8% for AHI ≥ 15 (2).

Patients suffering from moderate and severe OSA exhibit a range of comorbidities including cardiovascular disease, metabolic syndrome as well as depression. If their OSA is left untreated, the risk for all-cause mortality increases (3–6). Continuous positive airway pressure (CPAP) is a common treatment for OSA on the basis of its efficacy using objective mea-

sures (7). Despite its well-known benefits, adherence is generally poor and its use is often felt bothersome with little evidence on how its utility might be improved (8). It has therefore been deemed important to identify better tolerated treatment options (4).

Oral appliance (OA) treatment has long been used as measure against snoring and OSA. OA is in general inferior to CPAP in terms of reducing OSA parameters based on polygraphy especially in severe OSA. However, the greater efficacy of CPAP may not necessarily lead to a superior health outcome compared to treatment with OA. In this regard, it has been reported that OA adherence is in the range of 76% to 95%, which exceeds that of CPAP of which vary between 30% and 80% (9, 10). In contrast to CPAP, where data on adherence can be retrieved from device software, adherence to OA is usually self-reported and less accurate. However, in a recent report where adherence was measured via a built-in thermistor in the OA, 1-year results demonstrated a mean use rate of $6{\cdot}4 \pm 1{\cdot}7$ h per night in continuing users and a regular user rate of 83% (11). Consequently, OA adherence may actually be higher than for CPAP in treatment of OSA forming the basis for the suggestion of similar health outcomes on a group level for the two treatment modalities (12).

Oral appliance treatment is considered to be equally effective as CPAP in mild to moderate sleep apnoea, if titrated sufficiently (12–14). In severe OSA, CPAP is always the first-line treatment because it has a well-documented efficacy in reducing apnoeic events. Nevertheless, some studies report promising results even when using OA in patients with severe OSA (14–16). In addition, reports on antihypertensive effects and reduced cardiovascular mortality with OA treatment indicate a similar outcome to that of CPAP (17, 18).

The major risk groups for health complications among OSA patients are those with moderate and especially severe disease. Considering the high non-adherence rate to CPAP as well as the diverging results of surgical interventions (19), it is important to explore other conservative treatment alternatives more closely.

The aim of this study was to evaluate the effect of OA treatment in patients with moderate and severe OSA who were non-adherent to CPAP and to assess factors predicting treatment success/failure. Our hypothesis was that OA treatment was superior in patients with moderate compared to severe OSA.

Materials and methods

The baseline diagnosis of OSA and follow-up investigations were performed by respiratory medicine or ENT specialists at the Departments of Thoracic Medicine and Otolaryngology at Haukeland University Hospital, Bergen, Norway, supported by a medical examination that included home respiratory polygraphy (*). Sleep recordings were analysed by experienced respiratory medicine, and ENT specialists and scoring rules were in accordance with the 2007 American Academy of Sleep Medicine manual (20). The criteria for mild OSA were AHI 5–14·9, for moderate OSA $\geq$ 15–29·9 and for severe OSA AHI $\geq$ 30 (21). During the years 2007 to 2013, 127 consecutive patients were identified with a baseline diagnosis of moderate or severe OSA who had received OA treatment due to non-adherence to CPAP. Non-adherence to CPAP treatment was defined as less than 5 h usage/night during a period of at least three months (22, 23). All OA patients were treated by dentists with extensive training and experience in Dental Sleep Medicine.

Within the selected group of OA-treated OSA patients previously non-adherent to CPAP, inclusion criteria comprised subjects who had had a sleep study performed at baseline before CPAP and who attended the follow-up appointment including new sleep study using the OA ($n = 116$). The polygraphy recordings included AHI, oxygen desaturation index (ODI) and oxygen saturation parameters: mean ($SpO_{2\ mean}$), nadir ($SpO_{2\ nadir}$) and percentage time below 90% ($SpO_{2\ <90\%}$). Data on body mass index (BMI), previous snoring/OSA surgery, smoking habits and comorbidities, that is hypertension, other cardiovascular diseases, diabetes, were retrieved from the patients' medical records.

Success criteria

A successful OA treatment outcome was based on polygraphy at the follow-up and divided into three groups based on the following criteria: 1 = AHI < 5; 2 = 5 $\leq$ AHI < 10 and more than 50% reduction in baseline AHI; and 3 = AHI > 50% reduction in base-

Table 1. Criteria for treatment outcome with OA at follow-up polygraphy

Success criterion	AHI at follow-up
1	AHI < 5
2	$5 \leq$ AHI < 10 and more than 50% reduction in baseline AHI
3	>50% reduction in baseline AHI
4	$\leq$50% reduction in baseline AHI (failure)

AHI, apnoea hypopnoea index.

line AHI. If there was a $\leq$ 50% reduction in baseline AHI at the follow-up, the treatment was considered as a failure (Table 1).

Oral appliance treatment

Maxillary and mandibular impressions ([†]) and an occlusal protrusive wax or silicone index using George Gauge bite forkTM ([‡]) were made. The baseline fitting index of the OA was made at 50–80% of maximum protrusive capacity. The appliances were custom-made, and in the majority of patients a dual-block adjustable type (n = 89) ([§]) but in a few cases a generic-type non-adjustable mono-block appliance (n = 17) was delivered. The latter type of appliance was in several cases switched to the adjustable type in order to alleviate titration. Approximately 4–8 weeks after insertion of the appliance, the first evaluation of subjective effect was performed, and if not satisfactory, titration of the appliance was carried out. Titrations were performed until the patient reported a positive subjective effect (e.g. reduced sleepiness/snoring improved sleep) of the OA or until all possible adjustments were exhausted, after which follow-up objective overnight polygraphy was carried out.

Statistical analyses

Differences between the moderate and severe OSA groups and between treatment outcome groups (success or failure) were tested by means of the Mann–Whitney U-test. Wilcoxon signed rank test was used

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[‡]Great Lakes Orthodontics, Ltd., Tonawanda, NY, USA
[§]Somnodent®; SomnoMed Ltd., Crows Nest NSW, Australien or NarvalTM, ResMed Ltd., Bella Vista, NSW, Australia

to analyse intra-individual differences between baseline and follow-up regarding AHI, ODI and oxygen saturation parameters. Logistic regression analysis was performed with the most strict treatment success criteria applied as dependent variable at the follow-up (success: AHI < 5, failure: AHI $\geq$ 5). The following criteria were used for selection of independent variables: (i) theoretical relevance and (ii) significant findings according to Spearman correlation analysis between the dependent and the recorded baseline variables. All independent variables were dichotomized before entered into the regression model. Unadjusted and adjusted odds ratios were calculated. Additionally, forward conditional method was applied. Analyses to account for missing values were performed using multiple imputations. A P-value less than 0·05 was considered statistically significant.

Results

Of the 116 participants, 10 patients (8·6%) were lost to follow-up (three died and seven did not show up for their follow-up appointment). Thus, the total data set in the study included 106 patients (71 men, 35 women, mean = 57 year, range 28–90) who all had both a baseline and a follow-up polygraphy, except for two patients who reported non-adherence at the follow-up (recorded as failures). Seventy-four patients were diagnosed as having moderate OSA, and 32 patients had severe OSA. At baseline, there were no significant differences regarding age, BMI, gender, smoking habits and recorded comorbidities between the two severity groups (Table 2). Average time between the baseline sleep study and follow-up was 12 months (range 2–60 months, s.d. 11).

Baseline and follow-up AHI, ODI and SpO$_2$ parameters (average, nadir and percentage sleep time below 90%) in the two groups are shown in Table 3. The moderate group showed a significantly lower AHI (P < 0·01) and ODI (P = 0·01) at follow-up compared to the severe group. The average decrease in AHI units between baseline and follow-up was 15·8 and 32·2 in the moderate and severe group, respectively. The decrease in AHI units was significantly greater in the severe compared to the moderate group (P < 0·001). The percentage AHI decrease was however about the same in both OSA groups; moderate 76% and severe 79%, and not significantly different

Table 2. Baseline characteristics of the population studied: age, BMI, gender (males), commenced surgery (for snoring/OSA), smoking (present or previous) and comorbidities (smoking, hypertension, cardiovascular disease, diabetes) in the moderate (*n* = 74) and severe (*n* = 32) OSA groups

	Age (year) (s.d.)	BMI (s.d.)	Male gender, *n* (%)	Surgery, *n* (%)	Smoking, *n* (%)	Hypertension, *n* (%)	Cardiovascular, *n* (%)	Diabetes, *n* (%)
Moderate	57 (12·0)	28·2 (4·2)	46 (62)	32 (43)	27 (37)	34 (46)	13 (18)	8 (11)
	NS	NS	NS	NS	NS	NS	NS	NS
Severe	57 (12·2)	29·5 (4·3)	25 (78)	18 (56)	13 (41)	18 (56)	7 (22)	1 (3)

NS, not significant; BMI, body mass index.

Table 3. Apnoea hypopnoea index, ODI and oxygen saturation at baseline and follow-up in the moderate (*n* = 74) and severe (*n* = 32) OSA groups

	Moderate OSA					Severe OSA				
	AHI (s.d.)	ODI (s.d.)	SpO_2 mean (s.d.)	SpO_2 nadir (s.d.)	SpO_2 <90%	AHI (s.d.)	ODI (s.d.)	SpO_2 mean (s.d.)	SpO_2 nadir (s.d.)	SpO_2 <90% (s.d.)
Baseline	21·2 (4·0)	17·4 (8·0)	93·4 (1·5)	80·0 (5·9)	8·0 (9·3)	41·4 (9·9)	35·1 (14·2)	92·8 (2·5)	76·8 (4·8)	19·1 (17·8)
	***	***	NS	**	NS	***	***	NS	*	NS
Follow-up	8·1 (7·7)	7·8 (7·1)	93·4 (1·6)	83·1 (5·6)	6·5 (11·3)	17·4 (15·7)	14·9 (13·7)	92·6 (1·7)	80·6 (6·5)	13·8 (17·2)

AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; SpO_2 mean, mean oxygen saturation level; SpO_2 nadir, lowest oxygen saturation level; SpO_2 <90%, percentage of total sleep time with oxygen saturation level below 90%.
*$P < 0.5$; **$P < 0.01$; ***$P < 0.001$

Table 4. Apnoea hypopnoea index at follow-up and reduction in AHI units between baseline and follow-up in the moderate and severe OSA groups divided into successful and failed OA treatment

		n	Mean	Range	s.d.
Moderate OSA					
Success*	AHI at follow-up	57	5·0	0 to 13·5	3·1
	Decrease in AHI units	57	15·8	8·5 to 29·0	4·2
	Percentage reduction in AHI between baseline and follow-up	57	76	52·3 to 100·0	13·8
Failure†	AHI at follow-up	15	19·8	10·5 to 36·9	8·4
	Decrease in AHI units	15	2·2	−14·9 to 11·4	9·0
	Percentage reduction in AHI between baseline and follow-up	15	8	−71·4 to 47·9	41·3
Severe OSA					
Success*	AHI at follow-up	22	9·1	0 to 24·6	7·2
	Decrease in AHI units	22	32·2	21·4 to 49·7	8·1
	Percentage reduction in AHI between baseline and follow-up	22	79	50·8 to 100·0	14·2
Failure†	AHI at follow-up	10	35·7	17·5 to 67·7	13·7
	Decrease in AHI units	10	6·1	−6·0 to 18·2	7·6
	Percentage reduction in AHI between baseline and follow-up	10	15	−19·4 to 44·0	20·8

AHI, apnoea hypopnoea index.
*Success criteria: 1, 2 or 3.
†Failure criterion: ≤50% reduction in baseline AHI at the follow-up (Table 1).

between the two groups (Table 4). Self-reported adherence rate of the OA at the follow-up was 98% (104/106 patients).

The treatment success rate with the criterion 3 applied (>50% reduction in AHI) was 75% for the whole group (79/106 patients), comprising 77% and
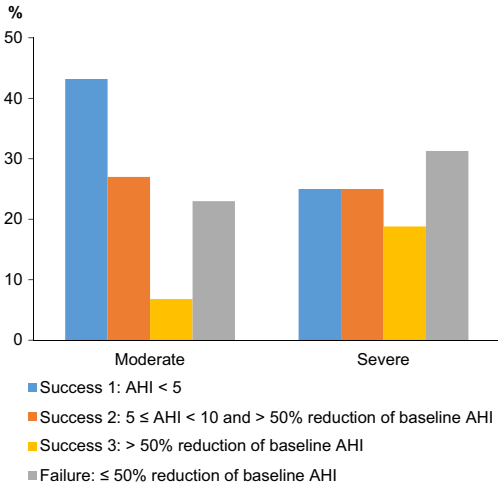
Fig. 1. Comparison between moderate ($n = 74$) and severe ($n = 32$) groups according to success criteria applied after treatment with oral appliance at follow-up.

69% of the moderate and severe groups, respectively. AHI < 5 (criterion 1) was recorded in 43% of patients in the moderate and 25% in the severe group, while it was 38% for both groups together. The combined figures for criteria 1 and 2 ($5 \leq$ AHI < 10 and more than 50% reduction in baseline AHI) were 70% and 50%, for the moderate and severe groups respectively. There was no significant difference in treatment outcome between the moderate and severe groups using the above-mentioned success criteria (Fig. 1). AHI at baseline and at follow-up after OA treatment in the successful group (criterion 1, 2 or 3, $n = 79$) and in the failure group ($\leq$ 50% reduction in baseline AHI at follow-up, $n = 25$) for each participant is shown in Fig. 2a and b.

In bivariate analyses between treatment outcome (success or failure) and baseline parameters, the success group, including both moderate and severe OSA, had lower prevalence of cardiovascular disease ($P < 0.05$), and a tendency for lower age and BMI

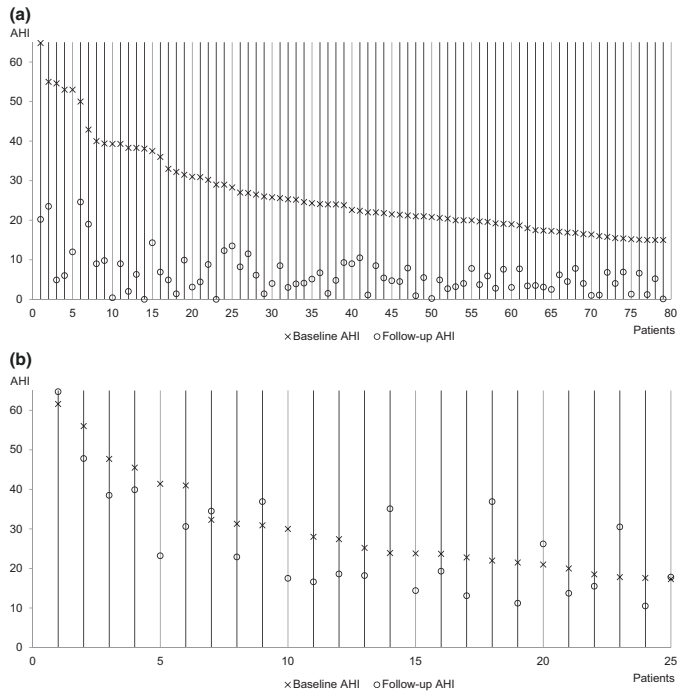**Fig. 2.** (a) Apnoea hypopnoea index at baseline and at follow-up after OA treatment in the successful group (criterion 1, 2 or 3 according to Table 1, $n = 79$). Patients are ordered from high to low baseline AHI. (b) AHI at baseline and at follow-up after OA treatment in the failure group ($\leq$50% reduction in baseline AHI at follow-up according to Table 1, $n = 25$). Patients are ordered from high to low baseline AHI.

(P = 0·075 and P = 0·05, respectively). Baseline AHI or gender did not differ between success and failure groups.

The outcome on the univariate evaluation of factors potentially predicting treatment failure is shown in Table 5, and the results from the logistic regression analyses are presented in Table 6. In the unadjusted analyses, all selected independent variables, except gender and $SpO_2{}_{<90\%}$, were significantly correlated to the success criteria applied, while in the fully adjusted analyses none of the variables predicted treatment failure/success. When applying the forward conditional method, $SpO_2{}_{nadir}$ turned out to be significant (OR = 0·36, p = 0·001) (Table 6); Nagelkerke R2 was 0·18 and the sensitivity (correctly classified successfully treated) and specificity (correctly classified failures) was 37% and 93%, respectively. The predicted probability for all variables and for $SpO_2{}_{nadir}$ is illustrated by the receiver operating characteristic (ROC) curve where the area under the curve (AUC) was 0·66 for $SpO_2{}_{nadir}$ while AUC for all the variables combined was 0·79 (Fig. 3).

The 10 patients lost to follow-up did not differ significantly compared to those who completed the study regarding age, gender, BMI, diagnosis (severe or moderate OSA), baseline AHI/ODI, snoring/OSA surgery, smoking habits, hypertension/cardiovascular diseases and diabetes.

Discussion

This retrospective study of 106 moderate and severe OSA patients non-adherent to CPAP showed an overall success rate of 75% using the criterion 3 (> 50% reduction in baseline AHI) (Table 1). This success rate compares favourably with that reported in recent reviews (9, 24), although most previous studies only included patients with mild to moderate OSA. Using the success criteria applied in this study, comparison of treatment outcome between the moderate and severe group showed no significant differences, albeit that a numerically higher proportion of patients reached AHI < 5 in the moderate group. What constitutes clinically acceptable success criteria for OSA treatment is much debated (9, 25). Although the moderate group had a significantly lower AHI (mean = 5) compared to the severe group (mean = 9) at follow-up, the latter experienced a considerably higher decrease in AHI units

Table 5. Correlations between success (AHI <5 at follow-up, n = 40) or failure (AHI ≥ 5 at follow-up, n = 66) and background variables and their dichotomizations

Baseline variables	Dichotomization	Success AHI <5	
		R	P
Gender	Man	0·07	0·5 (NS)
	Woman		
Age	≤69 year		
	>69 year	0·20	0·04
BMI	<27·5		
	≥27·5	0·23	0·02
AHI	15–25		
	> 25	0·20	0·04
ODI	≤20		
	>20	0·33	0·001
$SpO_2{}_{nadir}$	<85%	0·38	0·001
	≥85%		
$SpO_2{}_{<90\%}$	≥10%	0·24	0·04
	<10%		
Cardiovascular/	No		
diabetes disease	Yes	0·26	0·007

R, Spearman's rho; P, significance level; AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; $SpO_2{}_{mean}$, mean oxygen saturation level; $SpO_2{}_{nadir}$, lowest oxygen saturation level; $SpO_2{}_{<90\%}$, percentage of total sleep time with oxygen saturation level below 90%.

compared to the former (32 vs. 16 units). The clinical implication of this is unclear, but one may speculate that such a dramatic decrease of apnoeic events in the severe group may have a positive impact on health status even if not reaching the level of AHI < 5.

In category 2 success, it was required a 50% reduction in baseline AHI in addition to be below AHI 10 at follow-up. The reason for refinement of the criteria was that it was desired not only to appraise the cut-off point of 10 but also to make sure that the reduction had the commonly stated opinion that a 50% reduction in baseline AHI has a clinical benefit in the treatment of sleep apnoea patients (Table 1). There are only a few studies reporting on OA treatment of severe OSA. In this regard, and using similar criteria (> 50% reduction in baseline AHI) and follow-up time as in the present study, severe OSA treated with OA showed 44% (26) and 58% (14) success at 1-year follow-up. The higher success rate in this study (67%) may have several explanations, for example study design (retrospective study bias) and participant selections. When the most strict treatment success criteria

Table 6. Logistic regression analysis and associations between failure and success of OA treatment at follow-up (dependent variable: 1 = failure AHI ≥ 5; 2 = success, AHI < 5) and selected independent variables for unadjusted, adjusted and forward conditional models (Forward)

Independent variables	Unadjusted OR (CI)	P	Adjusted OR (CI)	P	Forward OR (CI)[†]	P
Gender						
Man = 1	0·73 (0·32–1·67)	0·45	0·74 (0·26–2·1)	0·57	*	
Woman = 2						
Age						
≤69 year = 1	6·7 (0·86–56·6)	0·07	9·8 (0·92–104)	0·06	*	
>69 year = 2						
BMI						
<27·5 = 1	2·6 (1·1–5·9)	0·02	2·1 (0·75–6·1)	0·16	*	
≥27·5 = 2						
AHI baseline						
15–25 = 1	2·3 (1·0–5·3)	0·04	0·67 (0·19–2·4)	0·54	*	
>25 = 2						
ODI baseline						
≤20 = 1	4·1 (1·7–9·9)	0·001	2·8 (0·73–11·0)	0·13	*	
>20 = 2						
$SpO_{2\ nadir}$						
<85% = 1	0·15 (0·04–0·54)	0·004	0·30 (0·07–1·3)	0·10	†	0·001
≥85% = 2						
$SpO_{2\ <90\%}$						
≥10% = 1	0·36 (0·12–1·1)	0·07	0·73 (0·20–2·7)	0·63	*	
<10% = 2						
Cardiovascular or diabetes disease						
No = 1	3·0 (1·3–6·8)	0·008	0·12 (0·005–2·1)	0·14	*	
Yes = 2						

OR, odds ratios; CI, 95% confidence intervals; P, significance level; Forward, forward conditional method; AHI, apnoea hypopnoea index; ODI, oxygen desaturation index; $SpO_{2\ mean}$, mean oxygen saturation level; $SpO_{2\ nadir}$ = lowest oxygen saturation level; $SpO_{2\ <90\%}$ = percentage of total sleep time with oxygen saturation level below 90%.
*Variable excluded in the final model.
[†]Variable included in the final model

were applied (AHI<5 at follow-up polygraphy), a number of baseline variables were significantly correlated to success in the unadjusted regression model. The anthropometric and polygraphic variables which have been reported as good predictors of successful OA treatment (9) are affirmative to those found in our unadjusted regression analyses (Table 6). In the adjusted model, none of the included variables turned out to be significant which may be explained of the inherent cross-correlations that exist between them and a reduced power in the analyses due to many variables in the model. However, in the final model (using the forward conditional method), only SpO_{2nadir} remained in the model with OR 0·36 demonstrating a low sensitivity (40%) but a high specificity (93%). It has been stated that more research is needed to define the patients who will benefit from MAD treatment (9) and it would also be

of significance to identify those who do not. Interpretation of the findings from the regression analyses may be that low oxygen saturation in OSA is an important predictor for OA failure in patients non-adherent to CPAP. This preliminary finding needs to be corroborated in future studies.

Patient categories with deep oxygen desaturations in conjunction with breathing cessations are typically those with pre-existing chronic diseases of the chest affecting gas exchange, such as chronic obstructive pulmonary disease (COPD), congestive heart failure and pulmonary hypertension. There is good evidence that oxygenation deficits rather than breathing cessations *per se* predicts mortality in patients with OSA (27). Furthermore, survival effects of positive airway pressure treatment in patients with OSA with chronic lung disease are documented (28), whereas research on OA treatment outcomes in COPD is lacking. The
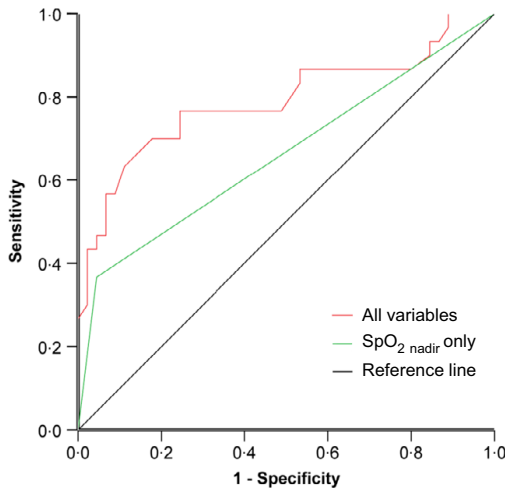
Fig. 3. Receiver operating characteristic (ROC) curve for SpO_2 nadir and for the full model including all variables in the regression analysis.

current results therefore support treatment with positive airway pressure methods, rather than OA treatment, in patients with severe oxygen desaturations from the diagnostic sleep studies, independent of OSA severity judged by the AHI only. However, it has to remembered that all participants where PAP-non-adherent and findings may not be generalized to the treatment decisions in treatment-naive patients with OSA.

Our definition of PAP non-adherence (less than 5 h per night over 3 months treatment) is based on publications demonstrating clinical meaningful responses on sleepiness, daily functioning and reductions in blood pressure in patients achieving at least 5–6 h adherence to CPAP per night (22, 23). In the current study, all participants have been treated with auto-CPAP devices, which automatically adjust the delivered pressures needed to avoid breathing cessations. No patients have been manually titrated in an overnight laboratory setting. Subjects with large desaturations at initial sleep study, who should be encouraged to PAP treatment despite adherence problems, could, when other causes of non-adherence have been excluded, undergo manually PAP titration in a sleep laboratory to ensure better treatment tolerance. In cases of CPAP non-adherence, other forms of pressure support such as bilevel or adaptive servo-ventilation

are often better accepted by subjects with chronic heart and lung disease.

The drawbacks of this study are several, and maybe the largest weakness is that we did not obtain adequate data related to subjective outcome of the treatment. Epworth Sleepiness Scale was recorded, but not consistently so in all instances. Details of adherence, such as number of nights and total hours of usage, to OA treatment was neither assessed which is another weakness but of the total of 116 patients who were prescribed OA treatment only two were recorded as non-adherent at the follow-up. Patients non-adherent to CPAP treatment are found to exhibit many barriers against its usage (29), and some of these may well be applicable to the use of an OA as well, although was apparently not so considering the seemingly high self-reported adherence of 98%.

Considering that the enrolled patients in this study were failures with the gold standard treatment for OSA (CPAP), we conclude that our results are very promising and especially so for severe OSA patients who are at greatest risks for serious medical consequences, if untreated. Low oxygen saturation (SpO_2 nadir) had a high predictive value for OA treatment failure irrespective of baseline AHI. Limited to the success criteria applied and to our surprise, the hypothesis that OA treatment is superior in patients with moderate compared to severe OSA was rejected. Future prospective and well-designed studies are warranted in order to confirm the findings from this study.

Acknowledgments

Ethical approval

The Regional Ethical Committee of Western Norway deemed the project not to require a formal ethical approval (protocol no: 2009/1229).

Conflict of interest

None.

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Paper II

II

ORIGINAL ARTICLE

WILEY | *Journal of* Oral Rehabilitation

Reliability of an adherence monitoring sensor embedded in an oral appliance used for treatment of obstructive sleep apnoea

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Summary

The aim of this study was to test whether digitally registered use of a mandibular advancement device (MAD) by a built-in thermal sensor was reliable compared to a self-reported diary of MAD use. Eighty consecutive patients referred to a specialist outpatient sleep medicine clinic (HUS) were recruited. Patients of both genders, aged from 25 to 70 years with a diagnosis of mild, moderate or severe, were included. All participants signed a written informed consent when they received the MAD. For the purpose of this reliability study, we found it sufficient to include the first 30 nights of MAD use in the reliability analysis. At the 30th night follow-up visit, the self-reported diary with duration of MAD use was returned and data on the duration of MAD use with the built-in sensor were retrieved. From a total of 2400 nights, complete data from both methods were retrieved for 2108 nights (84.6%). Missing data were largely a result of missing self-reported diaries, whereas technical failure occurred in 6 nights (0.002%). The relative reliability was very high with $ICC_{3,1}$ 0.847, and the absolute reliability for digitally registered MAD usage was calculated to −0.17 (95% CI: 1.47 to −1.81) hours in decimal conversion. Objectively collected data from built-in thermal sensors in MADs are as reliable as those of the self-report assessments. This opens new possibilities for more accurate measurements of MAD adherence.

KEYWORDS

adherence, continuous positive airway pressure, digital sensor, mandibular advancement device, obstructive sleep apnoea, reliability

1 | INTRODUCTION

Obstructive sleep apnoea (OSA) involves repeated cessations of breathing during sleep caused by obstruction of the upper airways. Recent studies report prevalence rates as high as 16%-50% in adult women and men.[1] OSA is associated with an increased risk of several comorbid conditions, for example cardiovascular diseases, stroke, asthma, gastro-oesophageal reflux, metabolic syndromes including obesity and diabetes type 2, in addition to a reduced quality of life.[2-6] Untreated OSA has a substantial socio-economic impact through raised healthcare costs, productivity losses and 2- to 10-fold increased risk of motor vehicle accidents.[7,8] All-cause mortality is increased in untreated OSA

patients,[9,10] and consequently, shortened life expectancy is reported for this patient group.[11]

Continuous positive airway pressure (CPAP) is the current gold standard treatment of OSA, but despite its well-documented positive effects, the adherence rate is low. A review of 50 years research on variations in patients' adherence to medical recommendations showed that the poorest rates of adherence were related to pulmonary diseases, diabetes and sleep disorders.[12] Most CPAP devices are fitted with an electronic timer, which registers time of use in addition to delivered air pressure, leakage and apnoea events, allowing for objective adherence records and feedback of treatment efficacy. The reasons for high non-adherent rates are manifold and may include practical

problems, negative psychological effects and attitudes to the treatment as well as side effects and insufficient support from healthcare personnel and the spouse.[13] Even though telemedicine platforms and mobile health applications are currently under study as promising tools improving CPAP adherence,[14] similarly effective and easier-to-use treatment options are important to develop.[15]

One alternative is a mandibular advancement device (MAD), which has been used against snoring and OSA for decades. MAD is in general inferior to CPAP in terms of reducing OSA parameters like apnoea hypopnoea index (AHI), especially in severe OSA. However, the greater objective efficacy of CPAP may not necessarily lead to a superior health outcome compared to treatment with MAD. Reports on MAD show a self-reported adherence range at 76%-95%, while the corresponding figures for CPAP vary from 30% to 80%.[16,17] However, it is important to develop reliable objective methods for measurement of MAD adherence, allowing for direct comparisons between CPAP and MAD treatment efficacy and subsequent health outcomes in properly designed studies.

Within other fields of odontology like orthodontics, treatment success is also largely dependent on adherence. The first attempt to measure wearing time of an orthodontic device was made about 36 years ago.[18] However, it has been very difficult to create wearing time sensors applicable in the everyday treatment use because of its bulky shape and inconvenience for the patients. But in 2010 a new microelectronic temperature sensor became available to the market of orthodontics, named Smart-Retainer (Austria), which permitted objectively measured wearing time.[19] At the same time, a German company also developed another wearing time measurement device named TheraMon. Reliability of this sensor was evaluated in thermostatic water bath before introduction to the clinic. This technology was developed into sensors built into MADs, which recently were tested in OSA patients.[20] Their one-year results demonstrated a mean use rate of 6.4 ± 1.7 hour/night in continuing users, defining wearing time as temperature higher than 35°C by the RespiDent Butterfly MRA thermistor. Relative reliability between subjective and objective measurement was expressed as Bland-Altman limits of agreement plots and intra-class correlation coefficient (ICC). However, although the time of MAD usage was reported, the absolute reliability was not calculated and the statistical power was fairly low. Thus, there seems to be a need for more detailed reliability analyses of MAD sensors, and particularly for newer sensors like the Braebon sensor (Figure 1) used in this study, which also offers new measurement possibilities on sleeping position and software algorithms for detecting non-adherence.

It is important to establish a reliable assessment of adherence to MAD in order to evaluate the treatment effect. Any objective measurement method needs to be tested for its reliability before it can be used in a broader scale. A reliability analysis of a measurement method should always include both absolute reliability and relative reliability.[21] Absolute reliability is calculated in the same scale and units as the method of measurement. Relative reliability is calculated as a unitless arbitrary value, which allows comparison across different scales and outcomes.

FIGURE 1 Photograph of the mandibular advancement device (MAD) with the built-in thermal sensor (DentiTrac®) used in this study

The aim of this study was to test whether digitally registered MAD use by a built-in sensor (Braebon) was reliable when compared to self-reported MAD use.

2 | MATERIALS AND METHODS

2.1 | Patient selection

At the Center for Sleep Medicine/Norwegian Competence Center for Sleep Disorders, Haukeland University Hospital, a specialist dental clinic has been established as part of the multidisciplinary team. OSA patients referred to the Center, who turned out to be non-compliant to CPAP, were invited to participate in the study. The statistical power needed in reliability studies is by convention usually set to a minimum of 50. In this perspective, we decided to enrol consecutive patients over a period of 12 months, which tentatively would include approximately 80 patients to have sufficient statistical power by a good margin.

2.2 | Inclusion criteria

Patients referred to a specialist outpatient sleep medicine clinic (HUS) were recruited consecutively until a convenience sample of n = 80 patients were included. Both genders were included with ages between 20 and 80 years. Patients with all OSA severities were included, that is mild (AHI = 5-14), moderate (AHI ≥ 15-29) or severe OSA (AHI ≥ 30).

2.3 | Exclusion criteria

Patients were excluded if they had severe periodontal disease, loss of teeth that compromised retention of the MAD, acute TMD problems, impaired cognition or lack of communication skills.

2.4 | MAD measurement methods

The selected MAD device (Somnodent Fusion®, SomnoMed Ltd., Crows Nest, NSW, Australia) was fitted with a built-in sensor/DentiTrac® (Braebon Medical Corporation, Kanata, ON, Canada). Registered data were retrieved from the chip and entered into a software developed by the manufacturer (Braebon Medical Corporation). The DentiTrac measures temperature to 0.1°C resolution along with spatial orientation/movement in the x-, y- and z-axis to 2°C resolution and head position. These data are used within a patented algorithm to accurately determine when the appliance is being worn (in the oral cavity) or not. The DentiTrac battery has a life span of approximately 5 years and has enough memory to store 6 months of data. The software can generate detailed reports presenting the duration of the appliance is being worn, and the per cent supine vs non-supine head position. In addition to the electronic data, patients were asked to self-report MAD use for each night on pre-formatted paper, in hours, with smallest value being 0.5 hours.

2.5 | Treatment procedure

The MAD treatment followed the standard procedure at the Department:

1. Delivery of the appliance. All participants signed a written informed consent.
2. Follow-up after 30 nights, 12 weeks, 6 months, 1 year and thereafter every 6th month.

For the purpose of this study, we found it sufficient to include the first 30 nights of MAD use in the reliability analysis. At the 30th night follow-up visit, a self-reported diary with a night-to-night duration of MAD use was returned by each patient. In addition, data from the use of MAD with the built-in sensor were retrieved from the software. The data consist of hours of MAD use each night and sleeping position, either supine or non-supine position.

2.6 | Costs and ethical considerations

The study followed the regular procedures of the clinic with very little inconvenience and no risk of adverse events for patients. The MAD devices are fully reimbursed for each patient through the National Health System in Norway. The additional costs for the sensors were covered by research grants from the University of Bergen, and no extra costs were imposed on the patient. Patients pay a consultation fee of NOK 345 to the hospital at each visit. The project was otherwise internally funded and received no financial support from manufacturers. The project outline was submitted to the regional ethical committee who concluded that the study was regarded as a quality assurance study, and a formal ethical approval was unnecessary (REK vest: Ref. no.: 2014/1613).

2.7 | Statistical analysis

Data were entered into a statistical software package (IBM SPSS Statistics for Windows version 24.0, IBM Corp. Armonk, NY, USA) by a person unaware of the results of self-reported data of MAD usage. The data were then analysed, and reliability was assessed by statistical methods such as $ICC_{3,1}$ and Bland-Altman limits of agreement for relative reliability. Absolute reliability was assessed as mean S_w (mean difference × 1.96 ± SD).

3 | RESULTS

The inclusion period lasted from August 2014 to November 2015. A total of 80 patients with an average age of 53.5 (±9.5) years (13 females and 67 men) with mild, moderate or severe were included.

However, in 23 patients (28.8%) data were incomplete and missing for at least one night. For four of these patients, data were missing due to technical failure of the built-in sensor during one or two nights, respectively. Missing data from lack of self-reporting for one or more nights were the most common reason for incompleteness. Still, both data from self-reporting and the built-in sensor were available for 84.6% of the total 80 × 30 nights = 2400 nights. As the pairwise comparison of outcomes from each night forms the basis for our statistical analysis of reliability, we decided to include all registered nights with paired self- and sensor-reported nightly usage (n = 2108 nights).

Every patient was interviewed and asked about problems associated with the sensor usage, but data from this question were not systematically stored. From our clinical observations, approximately only one in ten patients reported minor discomfort related to the bulkiness of the MAD sensor. Such discomfort was typically reported by smaller female patients with a small oral cavity. Most patients were otherwise positive to the trial and found it inspiring to contribute.

The use of MAD was normally distributed for both self-reported (Figure 2) and sensor-reported data (Figure 3). The mean self-reported MAD usage was 6.89 hours (±SD = 1.47), and the digitally registered MAD usage was 7.06 hours (±SD = 1.60 and ±SEM = 0.0348). The small difference in means of 10.2 minutes (0.17 hours ±SD 0.83, before conversion) or 4.2% was statistically significant (P < .01) due to the strong high statistical power (n = 2108). Absolute reliability for digitally registered MAD usage was calculated to −0.17 (95% CI: 1.47 to −1.81) hours in decimal conversion. Absolute reliability measured with 95% limits of agreement is also shown as a Bland-Altman plot in Figure 4. Correlation between self-reported and digital registered data measured with Pearson's r was highly significant (P < .001) with a linear and homoscedastic correlation appearance at r = .855 (Figure 5). The relative reliability was also high with an $ICC_{3,1}$ of 0.847 (95% CI: 0.834-0.859).

4 | DISCUSSION

The method used in this study could have some benefits especially for patients with cognitive impairment. It also opens the possibility of
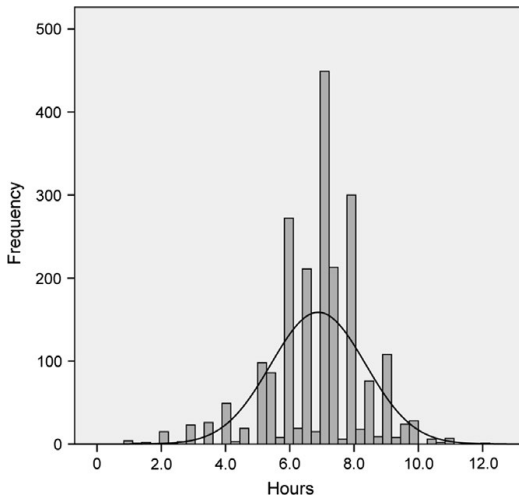
FIGURE 2 Distribution of results for self-reported time with mandibular advancement device (MAD) placed in the oral cavity. Hours and minutes expressed in decimal conversion
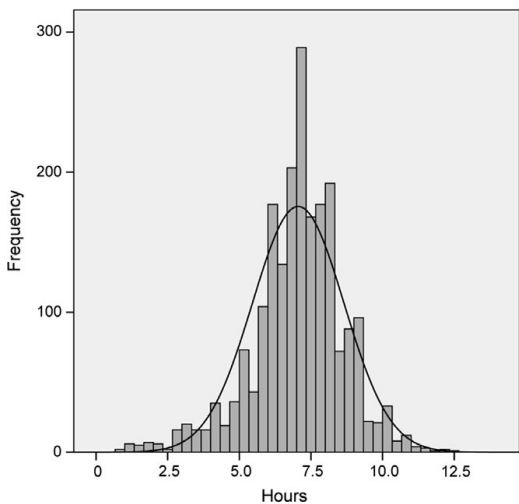

FIGURE 3 Distribution of results for digitally registered time by DentiTrac with mandibular advancement device (MAD) placed in the oral cavity. Hours and minutes expressed in decimal conversion

FIGURE 4 Bland-Altman plot describing the mean difference between self-reported mandibular advancement device (MAD) usage time and digitally registered time by DentiTrac with MAD placed in the oral cavity. The mean difference is represented by the line in the middle and the limits of agreement, and its respective 95% confidence intervals are the upper and lower lines

FIGURE 5 Correlation plot containing the pairwise plots of self-reported mandibular advancement device (MAD) usage time and limits of agreement and digitally registered time by DentiTrac with MAD placed in the oral cavity. Note the near-linear correlation and homoscedastic appearance of the plots, indicating that the correlation is not affected by the length of sleeping time

reducing errors and inaccuracies in self-reporting and provides data in legal cases and management of more complicated OSA.

The Braebon built-in sensor used in this reliability study measures temperature and triggers the timer when temperature exceeds 33 degrees Celsius. In addition, it contains a sensor, which can distinguish between sleeping positions, that is supine or non-supine. To register this ove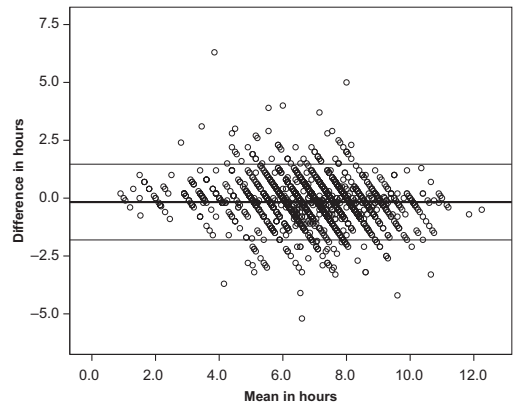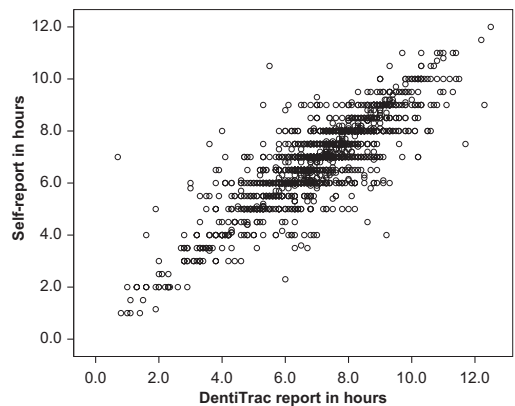r time during MAD use will be important when evaluating the home respiratory polygraphy in relation to supine/no-supine apnoea episodes. A new MAD with built-in sensor was recently introduced and included in a clinical study and sensor-reported use was consistent with self-reported use.[20] The data-storing capacity of their microsensor was limited to 100 nights, compared to the Braebon sensor that could store data for 180 nights. In addition, the latter sensor is able to distinguish between sleeping positions, that is supine vs non-supine, which was not possible for the microsensor used in the previously mentioned study.[20]

The patented algorithm Braebon developed uses the temperature and head movement data to accurately determine whether the appliance is in the oral cavity. The algorithm will compensate for mouth breathing and temporary significant rapid changes in the external environment as when drinking water. The feature of recording the percentage of time in supine and non-supine head position may serve as an aid to the clinician when treating patients with positional apnoea or those patients using the MAD where they have been advised not to sleep in supine position.

In our study, we found that digitally registered data from a MAD-built-in adherence sensor were highly reliable and deviated only by a mean of 10.2 minutes per night from the current standard of self-reporting. Whether this small difference was due to measurement errors in the self-reporting or digitally registered data may be determined in future studies perhaps in a sleep laboratory with independent observers. Nevertheless, it can be considered a weakness of our study design that we used retrospective self-reporting as a gold standard. On the other hand, and from a clinical point of view, a possible measurement error at 1/6 of an hour per night is far below the limits where non-adherence may influence the outcome of the MAD treatment. A strength of our study is that we recruited a large study sample well above the threshold needed for obtaining robust reliability results.[21]

It is important to remember that our study does not validate self-reporting as a gold standard or even as an accurate method of measurement of usage. In fact, we do believe that self-reporting may be fairly inaccurate, as reviewed by Sawyer et al[22] for CPAP treatment, reporting approximately 1 hour/night overestimation compared to objectively measured use. This needs to be investigated in a separate study with non-stop observation of MAD usage. Our study design is limited to address the reliability of sensor-registered data relative to a reference standard and not whether the gold standard is reliable or not.

From a reliability standpoint, we can conclude that subjective reporting and digitally registering can be used alternately in a short-term setting. On the other hand, as the patients in this study were aware that their own report would be thoroughly examined and compared to the sensor, this could have increased their adherence rate. In measuring long-term adherence, digital registration is therefore a prerequisite to avoid bias. A drawback is that we did not have a control device. The reason is simply that to our knowledge there is no fully validated adherence monitoring sensor available in the market.

The adherence to MAD has been suggested to be superior to that of CPAP. This challenges the superiority of CPAP effectiveness from a healthcare and economic point of view. According to a recent randomised controlled study, an economic analysis revealed that CPAP, even with a high adherence rate of 90%, had inferior cost-effectiveness vs MAD. The authors concluded that MAD was both cost-effective and clinically effective in mild-to-moderate OSAS.[23] It can therefore be speculated that MAD management of OSA patients will increase in the future. It may also become a prerequisite

that MAD should include objective adherence monitoring, and if so, such technologies should be more readily and commercially available for clinicians.

The new EU rules on driver licensing for patients with OSA[24] might require that MAD users have to objectively document their adherence in addition to its efficacy in order to retain their licence. In CPAP users, such information can easily be retrieved from the CPAP built-in software, but for MAD users, this has until now been impossible considering the lack of objective measurement methods. These new driving licence regulations represent a dramatic change for OSA patients. If they have daytime sleepiness and more than 15 breathing cessations per hour (AHI), effective treatment and documentation are required before they are allowed to take up driving again. As OSA is associated with increased risk for traffic accidents,[7] confirmation of effective treatment has to be certified by a relevant specialist. The adherence monitor chip in MAD allows the clinicians to gather information essential in the overall assessment of MAD treatment efficacy in relation to secure safe driving. Reliable methods of measurement of MAD use will be increasingly important as 8% of middle-aged elderly in Norway have an AHI > 15.[1] In this regard, long-term adherence with built-in sensor as used in this study is currently under way.

5 | CONCLUSION

Objectively collected data from built-in thermal sensors in MADs are as reliable as that of the self-report assessments. Adherence digital sensors could provide a novel way of obtaining, storing and documenting data on MAD adherence and opens for more reliable measurement of MAD use, and improved adherence-adjusted comparisons with other treatments.

ETHICAL APPROVAL

The project outline was submitted to the regional ethical committee who concluded that the study was regarded as a quality assurance study, and a formal ethical approval was unnecessary (REK vest: Ref. no.: 2014/1613).

CONFLICT OF INTEREST

The authors have stated explicitly that there are no conflict of interests in connection with this article.

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Paper III

III

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RESEARCH ARTICLE

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Partner perceptions are associated with objective sensor-measured adherence to oral appliance therapy in obstructive sleep apnea

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Summary

The aims of the present prospective clinical study were to determine objective, sensor-measured adherence to a mandibular advancement device (MAD) in patients with obstructive sleep apnea (OSA) and to identify partner-specific adherence-related factors. A total of 77 eligible participants with mild, moderate, or severe OSA and who were non-adherent to continuous positive airway pressure (mean age 56.2 years) participated in the study (32.5% women). The mean (range) observation time between MAD delivery and final follow-up was 8.3 (3.4–16.5) months. The mean apnea–hypopnea index (AHI) was 26.6 events/hr at baseline and 12.5 events/hr at the 8-month follow-up (both $p < 0.001$). The mean sensor-measured adherence at the 8-month follow-up was 60.1% for ≥4 hr/night of appliance use for ≥5 days/week. Average usage was 6.4 hr/night, when worn. The mean reduction in the AHI was significantly greater in the "good adherence" (Δ 17.4) than the "poor adherence" group (Δ11.0; $p < 0.05$). From the partner's perspective, the appliance had a positive effect on sharing a bedroom in the good- (55%) compared to the poor-adherence group (25%; $p < 0.05$) and on their relationship (51.7% versus 17.9%, respectively; $p < 0.05$). Regression analyses identified the partner's snoring and apneas to be the most significant factor predicting good adherence to MAD (odds ratio 4.4, 95% confidence interval 1.4–14.0). In conclusion, social factors, like partner perceptions, were positively associated with adherence, which indicate that partner's attitudes and support may be a resource that can be utilised to improve adherence in oral appliance treatment of OSA.

KEYWORDS
compliance, longitudinal, psychosocial factors, sleep apnea syndrome, titration

1 | INTRODUCTION

Obstructive sleep apnea (OSA) is associated with an increased risk of several conditions, e.g. cardiovascular disease, stroke, and metabolic syndromes, including obesity and diabetes mellitus type 2. OSA is also associated with a higher risk of traffic accidents, a reduced quality of life, and shorter life expectancy (Frangopoulos et al., 2020; Young & Collop, 2014).

Continuous positive airway pressure (CPAP) is considered the standard for treatment of OSA. When used, CPAP effectively alleviates obstruction, lowers the apnea–hypopnea index (AHI), and reduces other negative consequences of OSA (Wang et al., 2013).

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Poor adherence limits the efficacy of CPAP. One study reported no improvement in CPAP adherence in the last 20 years despite technological advances (Rotenberg et al., 2016). Common challenges in CPAP treatment include general discomfort with the equipment, nasal congestion, and leakage from ill-fitting masks (Genta et al., 2020). The patient's own motivation and partner support are also important (Shapiro & Shapiro, 2010). However, a recent meta-analysis shows that other, more comprehensive measures, like telemonitoring, seemed to improve CPAP adherence compared with usual care (Chen et al., 2020). Moreover, one study found cognitive measures, such as psychological support and disease-specific education, were strongly associated with adherence (Broström et al., 2018).

Mandibular advancement devices (MAD) are a simple, non-invasive alternative to CPAP (Ramar et al., 2015; Uniken Venema et al., 2020). Custom-made devices are preferred because they enable individual adjustments through titration. Another reason for recommending custom-made MAD is that the retention seems to be much less in non-custom-made MAD (Vanderveken et al., 2008). CPAP devices equipped with a memory chip are able to track adherence. Although not previously possible, recent studies report that MAD prototypes with monitoring sensors are able to record objectively measured adherence (Dieltjens et al., 2013).

Our knowledge of factors that can influence MAD adherence is limited, but several have been suggested. These include the relative ease of MAD use, the degree of discomfort, changes in the bite, snoring severity, and subjective sleep quality (Cayanan et al., 2019; Dieltjens et al., 2015; Marklund, 2020). Matching patient preferences with achievable lifestyle changes to find the most appropriate treatment design may also be important for improving adherence (Almeida et al., 2013). Nevertheless, the literature contains few studies on how OSA and its treatment affect social factors. Couples sleeping together in the same room might report that the quality of their relationship is high, which can be interpreted as a signal of intimacy and bonding. Many patients with OSA may be unaware of their nocturnal habits and how they negatively affect not only their sleep but also the relationship with their partner, e.g. sleeping in separate bedrooms (Richter et al., 2016). These patients could be motivated to use a MAD, seeing it as a way of sharing the bedroom again.

One retrospective study on the experiences of bed partners of patients with OSA reported improvements in general well-being, physical strength, and mental energy for both patients and bed partners after successful MAD treatment (Tegelberg et al., 2012). However, the design of the retrospective study had limitations: it recruited only successful responders, and the non-adjustable monobloc MAD that was used made titrations more difficult. Nevertheless, a systematic review in 2017 concluded that symptoms associated with OSA had a negative impact on the sleep and daytime functioning of partners (Luyster, 2017). Thus, further investigation of factors that could have an impact on MAD adherence is important.

The present prospective study investigated objective, sensor-measured adherence to MAD therapy and assessed whether bed partner perceptions affect MAD adherence.

2 | PATIENTS AND METHODS

2.1 | Patients

The present prospective study recruited 82 consecutive patients over 10 months from the Centre for Sleep Medicine at Haukeland University Hospital in Bergen, Norway. All patients and their partners signed an informed-consent form before entering the trial. Treatment outcome and adherence were determined at the final follow-up, ~8 months after the patient had received a MAD.

2.2 | Inclusion criteria

- Adult (aged ≥20 years).
- Diagnosis of mild OSA (AHI = 5–14.9 events/hr), moderate OSA (AHI = 15–29.9 events/hr) or severe (AHI ≥30 events/hr) OSA. Before study inclusion, all patients underwent a baseline clinical investigation with a lung or an ear, nose, and throat (ENT) specialist; the investigation included an overnight ambulatory respiratory polygraphy (RP; NOX-T3®, Nox Medical, Reykjavík, Iceland) to confirm the OSA diagnosis.
- Non-adherent to CPAP therapy. Non-adherence to CPAP was defined as <4 hr usage/night for ≥3 months (Weaver & Grunstein, 2008).

2.3 | Exclusion criteria

- Predominantly central sleep apnea
- Severe periodontal disease
- Loss of teeth that would compromise retention of a MAD
- Acute temporomandibular disorders

2.4 | Outcome measures

2.4.1 | Thermal sensor – adherence monitoring

A MAD (SomnoDent® Fusion, SomnoMed Ltd., Crows Nest, NSW, Australia) was custom-made for each participant and fitted with a sensor (DentiTrac®, Braebon Medical Corporation, Kanata, ON, Canada) that measured number of hours in use per night, temperature (lower cut-off value: 33°C), and head position (supine or non-supine). Braebon software summarised the observation period in a report that included hours of MAD use and percentage of time spent sleeping in either a supine or non-supine position. Adherence data were presented as follows: (a) device worn ≥4 hr/night, 7 days/week; (b) device worn ≥4 hr/night, ≥5 days/week; and (c) average daily use in hours, when worn. Criterion (b) was defined as acceptable adherence (Mullane & Loke, 2019). The Dentitrac chip has a battery capacity of ~5 years and enough memory to store data for up to 1 year. MAD adherence and average usage time were retrieved at the final follow-up.

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2.4.2 | Respiratory polygraphy

The AHI and oxygen saturation parameters (oxygen desaturation index [ODI], mean oxygen saturation [$SpO_{2\ mean}$], nadir oxygen saturation [$SpO_{2\ nadir}$], and percentage time <90% [$SpO_{2\ <90\%}$]) were collected at baseline and at the final follow-up. A nurse specialist with relevant education and extensive experience in RP scored the recordings at the Centre for Sleep Medicine at Haukeland University Hospital, Bergen, Norway. Polygraphic scoring followed the American Academy of Sleep Medicine guidelines for scoring events during sleep (Berry et al., 2012). The success criteria and failure criterion used to determine MAD therapy outcome at the follow-up were:

- Success criterion 1: AHI ≤5 events/hr
- Success criterion 2: AHI ≥50% reduction from baseline
- Failure: AHI <50% reduction from baseline

The RP recordings were made at baseline and ~3 and 6 months after the patient had received the MAD. If the subjective effect (e.g. better sleep, less daytime fatigue, less snoring) and RP parameters of the MAD treatment were satisfactory (according to the success criteria) at the 3-month follow-up, no more titrations were done. If the RP with the MAD was unsatisfactory or if the patient reported an inadequate treatment effect, the MAD was titrated until all possible variations in adjustments were exhausted, after which a final RP was carried out (between 6 and 8 months dependent on the patient's ability to meet for the consultation).

2.4.3 | Questions to patients and partners

The patients and their partners responded to the queries on social factors at baseline and at final follow-up. The questions at baseline queried if and how OSA had influenced their relationship and sleep, if they shared a bedroom, and if the partners could rate the intensity or volume of the patient's snoring. The questions at the follow-ups queried whether MAD use had had any positive or negative impact on their relationship, which factors did or did not motivate the patients to use their MADs, and if MAD use affected whether the patient and partner shared a bedroom (see Appendices S1 and S2 for questionnaire descriptions).

2.5 | MAD treatment

Baseline examinations and MAD manufacture followed standard procedures at the Centre for Sleep Medicine at Haukeland University Hospital in Bergen, Norway.

1. A clinical examination of the teeth, mucosa, and occlusal relations was made, and a functional examination of the chewing system comprised measurement of the vertical overbite, the horizontal overjet, maximum opening capacity, and horizontal movements.

2. The baseline position of the MAD appliance, when the patient held their bite in a position of maximum comfortable protrusion, was determined with a George gauge instrument.

3. Impressions of the upper and lower jaws (Xantasil® Kulzer GmbH, Hanau, Germany) along with the George gauge index were sent to the laboratory that manufactured the device (Somnodent®, Somnomed Nordic AB, Stockholm, Sweden).

4. The MAD was delivered and fitted in the patients ~4 weeks after the impressions were taken.

2.6 | Statistical analysis

We performed a sample size calculation of the statistical power before study start. We expected group (patients and bed partners) to be a strong predictor in the regression model. If this predictor alone explained 10% ($R^2 = 0.1$) of the total variance in total time of adherence, 73 individuals would be needed to obtain statistical differences (using a power of 0.8 and setting the level of significance at $p < 0.05$). If three variables (patient group, daytime sleepiness, and psychosocial factors) explained 15% ($R^2 = 0.15$) of the total variance in total time of adherence, 66 individuals would be needed. To account for drop-outs and other random variations, we decided to recruit ≥80 patients to the study.

Descriptive statistics were performed and the paired Student's t tests or the Wilcoxon signed-rank test were used for paired comparisons. The Mann–Whitney U test was used for between-group differences.

Good adherence, as recorded by the sensors, was defined as appliance use for ≥4 hr/night and (1) for ≥5 days/week, for ≥70% of the monitored weeks, (2) for ≥70% of all nights. Poor adherence was defined as appliance use for <70% of the monitored weeks or for <70% of all nights. An unadjusted model used multivariate analysis with logistic regressions and adherence (as defined in [2] above) as the dependent variable. Independent variables in the adjusted model were those found to be significantly correlated to adherence in the unadjusted analyses.

2.7 | Ethical considerations

The Ethics Committee of Western Norway (REKVest) approved the present study (daybook no. 2018/1771/REKVest) on December 14, 2018.

3 | RESULTS

3.1 | Baseline descriptive data

The present prospective study offered 82 consecutive patients who met the inclusion criteria participation. Five patients (6.1%) were lost to follow-up (three became ill, two did not show up); 77 patients

completed the study and were included in the statistical analyses. The final study group comprised 25 women and 52 men (mean [range] age 56.2 [31–82] years); 57 patients (74%) were cohabitating or married and 20 (26%) were single. At baseline, 22 patients (28.6%) were diagnosed with mild (AHI 5–14.9 events/hr), 30 (39.0%) with moderate (AHI 15–29.9 events/hr), and 25 (32.5%) with severe (AHI ≥30 events/hr) OSA. The mean (SD) baseline AHI was 26.6 (19.4) events/hr; 75% of the OSA patients and 70% of the bed partners reported that the sleep problems of the patients had a negative influence on their relationship.

3.2 | Outcomes after MAD treatment

3.2.1 | Adherence

The mean (range) follow-up time for sensor-measured adherence was 8.3 (3.4–16.5) months. The mean adherence based on the criterion "device worn more than ≥4 hr/night, 7 days/week" was 57.8% and based on the criterion "device worn ≥4 hr/night, ≥5 days/week" was 60.1%. Average use of MAD was 6.4 hr/night, when worn. Data retrieval from the built-in sensor was without any major difficulty except for five sensors that presented problems with readout and had to be replaced. The replacement of the sensors did not affect the adherence data retrieved from these patients.

3.2.2 | Respiratory polygraphy

Compared with baseline all recorded RP parameters were significantly lower at the follow-up (Table 1). The mean (SD, range) difference between AHI at baseline and the follow-up was 14.1 (7.1, −19.2 to 75.8) events/hr. In all, 16 (20.8%) patients fulfilled success criterion 1 (AHI <5 events/hr), 26 (33.8%) fulfilled criterion 2 (≥50% reduction of baseline AHI), and 35 (45.5%) were failures (<50% reduction of baseline AHI).

Comparisons between baseline and the final follow-up showed significant shifts toward lower categories of OSA severity overall (Figure 1) and in gender and civil status subgroups (Table 2).

3.2.3 | Partner and relationship perspective

A total of 55.9% of the patients expressed that partner support was "fairly" or "very" important for their MAD adherence. At the final follow-up, 67.2% of the bed partners reported that MAD use had a positive impact on their relationship.

3.2.4 | Good or poor adherence at the final follow-up

At baseline, none of the RP parameters differed significantly between the good adherence (appliance worn ≥70% of weeks from baseline to follow-up, $n = 37$) and the poor adherence (appliance worn <70% of weeks from baseline to follow-up, $n = 40$) groups. However, at the follow-up, AHI, ODI, $SpO_{2\,nadir}$ and the change in AHI from baseline to follow-up (ΔAHI) were significantly more improved in the good- compared to the poor-adherence group (Table 3). No such between-group differences were detected regarding gender, age, civil status, $SpO_{2\,mean}$, or $SpO_{2\,<\,90\%\,sleeping\,time}$ (data not shown). In the poor-adherence group, 60.0% were failures compared to 29.7% in the good-adherence group ($p < 0.05$). Although the distribution of OSA severity showed no significant differences between the good- and poor-adherence groups at baseline, OSA severity had improved significantly more at the follow-up in the good-adherence group than the poor-adherence group ($p < 0.05$).

Compared to the good-adherence group, the poor-adherence group reported more frequently that the MAD was uncomfortable to wear (22.5% versus 5.4%, $p < 0.05$), that it was difficult to use during sleep (12.5% versus 0%, $p < 0.01$), and that they had forgotten to insert it when they went to sleep (40.0% versus 13.5%, $p < 0.05$; data not shown). Table 4 presents findings from the partner perspective questionnaire on MAD use. Partners with a participant in the good-adherence group reported more positive treatment effects, leading to sharing the bedroom ($p < 0.05$), and on the relationship in general ($p = 0.01$) compared with partners living with a patient in the poor-adherence group (Figure 2).

TABLE 1 Respiratory polygraphic recordings at baseline and at the final follow-up

	Baseline			Follow-up			
	Mean	SD	Range	Mean	SD	Range	P
AHI	26.6	19.4	6.0–91.8	12.5	11.6	1.3–77.6	<0.001
ODI	27.4	18.5	6.7–85.6	13.8	12.0	1.2–78.6	<0.001
$SpO_{2\,mean}$	92.0	83.2	83.2–95.4	92.5	2.0	85.1–95.8	<0.01
$SpO_{2\,nadir}$	80.6	6.8	54.0–89.0	83.0	5.7	63.0–92.0	0.001
$SpO_{2\,<\,90\%}$	15.0	22.6	0.0–91.2	9.4	19.9	0.0–98.5	0.01
Snoring	21.5	16.5	0.0–58.4	15.2	17.9	0.0–75.8	0.001

AHI, apnea–hypopnea index; ODI, blood oxygen desaturation index; $SpO_{2\,mean}$, mean blood oxygen saturation in percent; $SpO_{2\,nadir}$, lowest blood oxygen saturation in percent; $SpO_{2\,<\,90\%}$, percentage of total sleep time below 90% blood oxygen saturation; Snoring, percentage of total sleep time.
p denotes the significance in the difference between baseline and follow-up (paired samples t test).
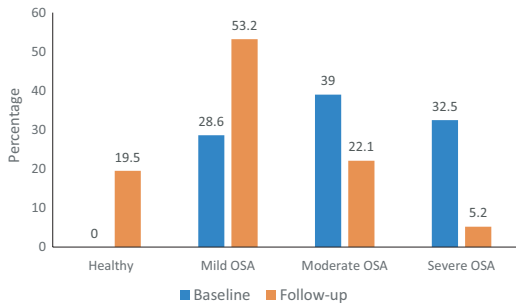
FIGURE 1 Distribution of obstructive sleep apnea (OSA) severity among non-adherent continuous positive airway pressure (CPAP) patients (n = 77) at baseline and at the final month follow-up

3.2.5 | Partner perspectives - logistic regression

In the unadjusted logistic regression, three questionnaire variables were significantly correlated with good adherence: (1) "My sleeping problem makes my partner tired during daytime" (Yes), (2) "My partner's snoring and breathing cessations keep me awake at night" (often), and (3) "How do you experience the volume of your partner's snoring?" (visual analogue scale [VAS] 1–10). However, in the adjusted model, only question no. 2 remained significant (odds ratio 4.4, 95% confidence interval 1.4–14.0; Table 5).

4 | DISCUSSION

The present prospective study of 77 patients with diagnoses ranging from mild to severe OSA measured objective adherence to MAD

TABLE 2 Severity of obstructive sleep apnea (OSA) at baseline and during therapy with a mandibular adjustment device (MAD) at the final follow-up in the total sample (n = 77) and according to gender and marital status

	OSA at baseline, n (%)			Healthy, n (%)	OSA at the follow-up, n (%)			p
	Mild	Moderate	Severe		Mild	Moderate	Severe	
Total (n = 77)	22 (28.6)	30 (39.0)	25 (32.5)	15 (19.5)	41 (53.2)	17 (22.1)	4 (5.2)	<0.001
Gender								
Men (n = 52)	16 (30.8)	20 (38.5)	16 (30.8)	7 (13.5)	33 (63.5)	9 (17.3)	3 (5.8)	<0.001
Women (n = 25)	6 (24.0)	10 (40.0)	9 (36.0)	8 (32.0)	8 (32.0)	8 (32.0)	1 (4.0)	<0.001
Marital status								
Cohabiting/married (n = 57)	17 (29.8)	21 (36.8)	19 (33.3)	10 (17.5)	31 (54.4)	13 (22.8)	3 (5.3)	<0.001
Single (n = 20)	5 (25.0)	9 (45.0)	6 (30.0)	5 (25.0)	10 (50.0)	4 (20.0)	1 (5.0)	0.001

The p values denote the differences between baseline and the final follow-up (Wilcoxon signed-rank test).

TABLE 3 Comparison of the patient groups with good versus poor adherence based on the criterion that the mandibular adjustment device (MAD) had been worn "≥4 hr/night, ≥5 days/week"

	Good[a] (n = 37)			Poor[b] (n = 40)			
	Mean	Range	SD	Mean	Range	SD	p
AHI–baseline	27.8	6.8–70.6	18.7	25.5	6.0–91.8	20.2	NS
AHI–follow-up	10.4	1.3–77.6	12.3	14.5	1.4–53.3	10.8	0.03
ODI–baseline	28.8	6.7–72.6	17.6	26.1	7.1–85.6	19.5	NS
ODI–follow-up	11.7	1.2–78.6	12.4	15.8	1.4–57.3	11.4	0.03
$SpO_{2\,nadir}$–baseline	80.7	54.0–89.0	7.7	80.5	63.0–87.0	6.0	NS
$SpO_{2\,nadir}$–follow-up	84.1	64.0–91.0	5.4	82.0	63.0–92.0	5.8	0.03
AHI Δ[c]	17.4	−19.2–65.3	18.2	11.0	−5.0–75.8	15.7	0.04

AHI, apnea–hypopnea index; ODI, blood oxygen desaturation index; $SpO_{2\,nadir}$, lowest blood oxygen saturation in percent.

p denotes the significance of the difference between the good- and poor-adherence groups (Mann–Whitney U test).

[a]MAD appliance worn ≥70% of weeks from baseline to final follow-up.

[b]MAD appliance worn <70% of weeks from baseline to final follow-up.

[c]AHI difference between baseline and the final follow-up.

TABLE 4 Distribution of answers (%) in the good- (n = 29) and poor-adherence (n = 28) groups at the final follow-up to the questions on how use of the mandibular adjustment device (MAD) affected (a) sharing the bedroom and (b) their relationship

	Good[a], %			Poor[b], %			
	Negative or not at all	Slightly positive	Very positive	Negative or not at all	Slightly positive	Very positive	p
How does your partner's use of the MAD affect whether you share a bedroom (partner perspective)?	27.6	17.2	55.2	46.4	28.6	25.0	0.04
To what extent does your partner's use of the MAD affect your relationship (partner perspective)?	20.7	27.6	51.7	46.4	35.7	17.9	0.01

p denotes the significance of the difference between the good- and poor-adherence groups (Mann–Whitney U test).

[a]MAD appliance worn ≥70% of weeks from baseline to follow-up.

[b]MAD appliance worn <70% of weeks from baseline to follow-up.

treatment using a SomnoDent Fusion oral device and a built-in DentiTrac sensor. Adherence data were collected for an average of 8.3 months. In a previous study on 30 nights with MAD and using the same compliance tracking recorder (DentiTrac) as in this study, the
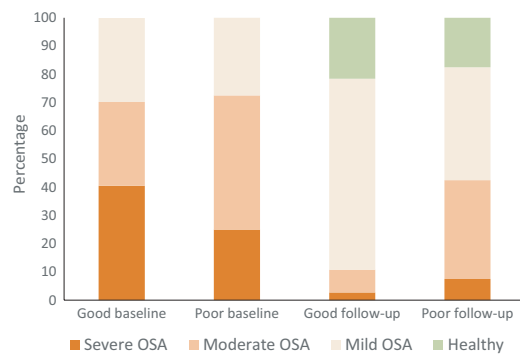

FIGURE 2 Obstructive sleep apnea (OSA) severity at baseline and at the final month follow-up in the good and poor compliance groups based on the criterion that the mandibular adjustment device (MAD) had been worn "≥4 hr/night, ≥5 days/week"

intraclass correlation coefficient was 0.85 compared to self-reports. This finding indicated a high correlation between self-reported and sensor-reported adherence (Gjerde et al., 2017). Similarly high correlations between subjective and objective adherence using another type of sensor (TheraMon microsensor, Austria) have also been reported (Dieltjens et al., 2013; Vanderveken et al., 2013). In addition, a high correlation was found between the DentiTrac sensor used in the present study and a different type (TheraMon microsensor) of built-in MAD sensor during a 3-month observation period (De Vries et al., 2017). This recent technological advancement in data storage and the sensor's feasibility to objectively measure MAD adherence for longer periods pave the way for more extensive use in clinical practice.

In light of this relatively new technology, we wished to further explore factors affecting adherence and speculated that partner involvement, shown to be important among CPAP users, might be significant (Baron et al., 2020). At the time of the present study, we had found two publications that addressed this aspect in MAD users; Tegelberg et al. reported that MAD use had a positive impact on the bed partner (Tegelberg et al., 2012), and Dieltjens et al. reported that partner reported decrease in social snoring correlated significantly with objective adherence (Dieltjens et al., 2015). Our present study

TABLE 5 Unadjusted and adjusted (forward conditional) logistic regression models predicting good or poor adherence to the mandibular adjustment device (MAD) in patients with a partner (n = 57). Adherence was dichotomised into (1) good (n = 23)[a] and (2) poor (n = 34)[b]

	Unadjusted		Adjusted	
Independent variables	OR (95% CI)	p	OR (95% CI)	p
My sleeping problem makes my partner tired during daytime (yes)	4.5 (1.3–15.6)	0.02	–	–
My partner's snoring and breathing cessations keep me awake during night (often)	4.4 (1.4–14.0)	0.013	4.4 (1.4–14.0)	0.013
How do you experience the volume of your partner's snoring? (VAS 1–10)[c]	1.4 (1.1–1.8)	0.02	–	–

Abbreviations: CI, confidence interval; OR, odds ratio; VAS, visual analogue scale.

[a]Appliance use ≥4 hr/night and ≥70% of all nights.

[b]Appliance use ≥4 hr/night and <70% of all nights.

[c]VAS, 0 = no sound; 10 = very high sound.

found similar results, that good adherence to MAD treatment had a positive effect on the relationship and was conducive to sharing the bedroom. We believe that these findings are indicative of the largely positive influence of partners on MAD adherence.

In the unadjusted analyses we identified three factors that could account for partner perspective: "My sleeping problem makes my partner tired during daytime", "How do you experience the volume of your partner's snoring?", and "My partner's snoring and breathing cessations keep me awake during night". The first two questions seem plausible factors that would affect adherence, but in the adjusted analysis, only the last question on snoring and apnea was significant. This finding is not unexpected, but again shows that partner perceptions are important and that the substantial effect of the MAD on socially disturbing snoring may be a stronger driver for high MAD adherence than improvements in objectively recorded RP parameters (Dieltjens et al., 2015).

Bed partners are a potential resource that could be tapped at the beginning of a long-term treatment programme with MAD. Perhaps clinics that manage patients with sleep apnea should invite partners to education lessons and advisory consultations along with the patients? One important question is obvious; would MAD adherence improve with more guidance and partner support, and perhaps a built-in reminder alarm in the device? Studies have found that information to patients on OSA in its early stages often improves CPAP adherence and outcomes (Broström et al., 2018; Chen et al., 2020). Thus, a similar approach in MAD therapy may improve quality of life for patients and help resolve the somatic and cognitive symptoms that frequent users of MAD often report (Nordin et al., 2016). Nevertheless, more research is needed to identify barriers for MAD use and to explore ways of improving adherence.

Adherence to MAD use in the present study was considerably lower (60.1% based on the criterion ≥4 hr, ≥5 nights/week) than reported in other studies. Earlier studies using the same criterion have reported adherences of 94.1% after 3 months, 100% after 12 months (de Ruiter et al., 2020), and 82% after 3 months (Dieltjens et al., 2013; Vanderveken et al., 2013). The patients in these studies had not previously tried CPAP treatment before entering MAD therapy. However, another study that did consider previous treatment with CPAP reported objective adherence to MAD in CPAP-intolerant patients using the same criterion as we did: 26% after 1 week and 50% after 4 weeks (Mullane & Loke, 2019). These results cite lower adherence than the present study found. Consequently, it seems that patients who were previously non-adherent to CPAP demonstrate lower adherence to MAD than patients who have not tried CPAP. The reason for this is unknown, but one suggestion is that patients who exhibited no treatment adherence to CPAP score higher on psychosocial issues such as claustrophobia, non-compliant personality, alcohol or drug abuse, and psychiatric disorders (Lin et al., 2007). Similar barriers may exist for non-adherent CPAP patients when using a MAD and might explain the relatively low adherence rate compared to that found in unselected patients with OSA.

When worn, average MAD usage per night in the present study was 6.4 hr, close to normal sleep duration. This is in line with other studies, e.g. 6.6 hr (Vanderveken et al., 2013) and 5.5 hr (Mullane & Loke, 2019). One study comparing usage of CPAP and MAD reported 1 hr longer nocturnal MAD usage (De Vries et al., 2017). The longer usage time and generally greater adherence in MAD therapy might be one explanation for the similar health outcomes between MAD and CPAP therapies, despite the greater efficacy of the latter (Dieltjens & Vanderveken, 2019; Sutherland & Cistulli, 2019).

Only a few published reports discuss factors affecting objective adherence to MAD treatment. One study found that decreased snoring was the only factor that positively affected usage: dry mouth had a negative impact on MAD usage; anthropometric and polysomnographic parameters, and reports of excessive daytime sleepiness, were not significantly correlated with MAD adherence (Dieltjens et al., 2015). Another study reported that side-effects, such as excess salivation, xerostomia, and tooth discomfort from use of the device, negatively influenced objective MAD adherence (Mullane & Loke, 2019). In general, the findings of these two studies are in line with those of the present study.

We divided the participants into two groups according to their degree of adherence: "good" and "poor". Factors that had a negative impact on usage were discomfort using the MAD, difficulties to use during sleep, and simply forgetting to use it at bedtime. Finding the device bothersome to use or sleeping alone might make patients more prone to forget it or even to take a break from using the MAD on purpose, which would explain the last factor. Nevertheless, the findings in the present study agree with the foregoing reports that side-effects are important for MAD adherence. Therefore, it needs to be stressed that the quality of the appliance is important, and that the clinician needs to follow the patient closely, especially in the first period after delivery of the MAD and adjust the device to minimise any side-effects.

At baseline, most patients in the present study had substantial respiratory dysfunction during sleep, and more than two-thirds were categorised with moderate or severe OSA. After the study cohort had used the MAD for an average of 8.3 months the mean AHI declined from 26.6 to 12.5 events/hr, and the percentage of patients with severe OSA dropped from 32.5% to 5.2%. It was encouraging that our present data yielded clinically relevant treatment results for the most severe group, supporting the findings of our previous study (Gjerde et al., 2016). In the present study, the treatment effects recorded at the final follow-up, such as a considerable shift in OSA category to one of lesser severity, were clinically relevant compared with baseline measurements. Nearly one in five patients became free of OSA symptoms (healthy: AHI ≤5 events/hr) during MAD use, while five out of six patients in the severe OSA group, shifted to a less severe category. It was also striking that the good-adherence group had a significantly lower AHI and ODI at the follow-up compared to the poor-adherence group. The reduction in AHI between baseline and the follow-up was ~50% greater in the good- (AHI Δ17.4) than in the poor-adherence (AHI Δ11.0) group. It is not clear whether good adherence to MAD treatment improves RP parameters compared with those of occasional users. Perhaps more regular use produces a

cumulative effect in the airways, resulting in a lower tendency to collapse, and thereby a greater reduction in AHI and blood oxygen saturation parameters? Another speculation is whether being given information (e.g. about significant reductions in AHI compared with the RP recordings taken during the MAD titration phase) helps promote good adherence? Nevertheless, this finding strongly underlines the importance of finding ways to promote and secure good adherence with MAD treatment.

4.1 | Strengths and limitations

A strength of the present study was the novel focus on bed partner perceptions, interactions, and associations with MAD adherence. The prospective design with almost no missing data is also a strength, and the use of predetermined outcome measures over a long, observation period (8.3 months). In addition, the study cohort represented a cross-section of all severity levels of OSA, including severe OSA. Another strength was that the sensor-registered adherence data, calculated by the software, secured objective measures. A limitation in our present study is the lack of a control group, but the design made it difficult to include controls in a sensible way in order to improve study quality. Another limitation was the lack of a standardised and validated questionnaire for MAD adherence. To the best of our ability, we constructed our own questionnaire, but it has not yet been validated. The literature has validated that in-hospital polysomnography (PSG) is the most accurate examination method of choice for OSA diagnostics, but studies have shown that ambulatory RP, as the NOX-T3$^®$ used in the present study, is not inferior to PSG for diagnosing OSA and requires less resources (Berry et al., 2008; Rosen et al., 2012; Kuna et al., 2011).

5 | CONCLUSION

The present prospective study confirmed that MAD adherence can be measured objectively with the built-in sensor for a period of 8.3 months, and that reduction in breathing cessations correlates positively with the degree of MAD adherence. Partner perceptions of snoring and apneas during the night are positively associated with adherence, suggesting that partner attitudes and support may be a resource that could help improve MAD adherence.

AUTHOR CONTRIBUTIONS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

Appendix: Questionnaires

IV

Spørsmål til apneskinnepasienter

(Besvares ved apneskinne tilpasning **før** oppstart av behandlingen)

1) Sivil status: Gift/samboer ☐ Enslig ☐

2) Hvis du har samboer eller er gift; sover dere på samme soverom?

(sett kryss)

☐ alltid
☐ som oftest ☐ av og til
☐ sjelden
☐ aldri

3) I hvor stor grad virker ditt søvnproblem inn på parforholdet?

(sett kryss)
svært stor grad☐ stor grad☐ til en viss grad☐ ikke i det hele tatt ☐

4) På hvilken måte virker ditt søvnproblem inn på parforholdet?

(sett kryss - flere kryss er mulig)

☐ det holder din partner våken
☐ det gjør din partner trøtt og uopplagt på dagtid
☐ søvnen din blir urolig pga snorking og/eller pustestopp
☐ du føler deg uopplagt på dagtid
☐ du blir lett irritert og i dårlig humør
☐ du har lite energi til fysisk aktivitet og/eller sosialt samvær
☐ ditt søvnproblem har ingen innvirkning på samlivet/parforholdet

Spørsmål til apneskinnepasienter

(Besvares ved 3.mnd og 6.mnd kontroll av apneskinne)

5) Hvor ofte bruker du din apneskinne? (sett kryss)

☐ hver natt og mer enn 5 timer
☐ hver natt og mindre enn 5 timer ☐ mer enn 50% av nettene
☐ mindre enn 50% av nettene

6) Hvilke av disse faktorene motiverer deg til skinnebruk?

(sett kryss, flere kryss er mulig)

☐ mindresnorkelyd
☐ færrepustestopp
☐ mindredagtrøtthet
☐ får sove på samme rom som partner ☐ mindre sjenanse for
partner

7) Hvilke av disse faktorene hindrer deg i skinnebruk?

(sett kryss, flere kryss er mulig)

☐ ☐ ☐ ☐ ☐ ☐ ☐

glemmer å ta den på
glemmer å ta den med på reise
føles ukomfortabel å bruke vanskelig å sovne med den i munnen

opplever ingen effekt av den ømhet i tenner og/eller kjeve

andrefaktorer?...

For deg som deler soverom med andre gjelder spørsmål 8-10

8) Hvordan virker din bruk av apneskinnen inn på om dere deler soverom? (sett kryss)

☐ veldig negativt
☐ litt negativt

☐ ingen innvirkning ☐ litt positivt
☐ veldig positivt

9) Hvor viktig er partners støtte for om du bruker din apneskinne? (sett kryss)

Ikke viktig ☐ Litt viktig ☐ Nokså viktig ☐ Svært viktig ☐

10) Hvordan virker apneskinnebruken din inn på parforholdet?

☐ ☐ ☐ ☐ ☐

veldig negativt

litt negativt ingen innvirkning litt positivt
veldig positivt

(sett kryss)

Spørsmål til partner som lever med apneskinnebruker

(Spørsmål 1-4 besvares ved oppstart av skinnebruk)

1. **1) Hvordan virker din partners søvnproblem inn på parforholdet? (sett kryss)**

   Ingen innvirkning ☐ Litt negativt ☐ Svært negativt ☐

2. **2) På hvilken måte virker din partners søvnproblem inn på parforholdet? (sett kryss)**

   - ○ - Har din partners søvnproblemer innvirkning på parforholdet? aldri ☐ sjelden ☐ ofte ☐
   - ○ - Din partners søvnproblem gjør at du holdes våken med snorkelyd og/eller pustestopp.
     aldri ☐ sjelden ☐ ofte ☐
   - ○ - Din partners søvnproblem gjør at du våkner opp flere ganger i løpet av natten.
     aldri ☐ sjelden ☐ ofte ☐
   - ○ - Din partners søvnproblem gjør at du føler deg trøtt og uopplagt på dagtid.
     aldri ☐ sjelden ☐ ofte ☐
   - ○ - Din partners søvnproblem gjør at du lett kan bli irritert og i dårlig humør fordi du er trøtt.
     aldri ☐ sjelden ☐ ofte ☐

3) Hvordan opplever du lydstyrken av din partners snorking ?

Ingen lyd Svært kraftig lyd _____

0 1 2 3 4 5 6 7 8 9 10 (sett kryss på linjen)

4) Hvor ofte i løpet av natten er snorkelyden og/eller pustestoppene et problem for deg?

aldri om natten ☐ deler av natten ☐ store deler av natten ☐

Spørsmål til partner som lever med apneskinnebruker

(Spørsmål 5-8 besvares etter 3mnd og 6mnd bruk)

5) Hvordan har din partners bruk av apneskinne innvirkning på om dere deler soverom? (sett kryss)

veldig negativt ☐ litt negativt ☐ ingen innvirkning ☐ litt positivt ☐ veldig positivt ☐

6) Hender det at du minner din partner på å bruke apneskinnen?

(sett kryss)
aldri ☐ sjelden ☐ av og til ☐ nokså ofte ☐ svært ofte ☐

7) I hvilken grad virker din partners apneskinnebruk inn på parforholdet?
(sett kryss)

veldig negativt ☐ litt negativt ☐ ingen innvirkning ☐ litt positivt ☐ veldig positivt ☐

8) Hvis positiv innvirkning på parforholdet i sp. 7; kan det bety at:

(sett kryss)
apneskinnen gjør at dere kan sove på samme soverom?

ofte ☐ av og til ☐ aldri ☐
apneskinnen gjør det lettere å konsentrere seg og arbeide?

ofte ☐ avogtil ☐ aldri ☐

din partner og du har mer energi til fysisk aktivitet og sosialt samvær? ofte ☐ avogtil ☐ aldri ☐

uib.no